Prostate Cancer Foundation of Australia

RESEARCH AWARENESS SUPPORT

2025 Guidelines for the Early Detection of Prostate Cancer in Australia.

Clinical Practice Guidelines for Health Professionals

Technical report

2025

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List of abbreviations

Abbreviation	Definition
EAP	Expert advisory panel
MCID	Minimal clinically important difference (See 2.2.3.7)
NHMRC	National Health and Medical Research Council
PECO	Population, exposure, comparator, outcome (research question format)
PICO	Population, intervention, comparator, outcome (research question format)
PCFA	Prostate Cancer Foundation of Australia
PSC	Project Steering Committee
WG	Working group

1 Introduction

This Technical Report accompanies the *2025 Guidelines for the early detection of prostate cancer in Australia*, developed by Prostate Cancer Foundation of Australia (PCFA) with technical support and expertise from the Daffodil Centre, a joint venture between The University of Sydney and Cancer Council NSW, Australia. The report outlines the processes and methodology used to develop the clinical recommendations including the development of clinical questions, data extraction and assessment of quality, the evidence to decision process, drafting of recommendations and determination of strength of recommendations. For each clinical question, a detailed systematic review report can be found in Section 3.

2 Guideline development processes and methods

2.1 Processes

2.1.1 Guideline development team

Following a consultation process with key stakeholders involved in cancer control and clinical care delivery, including the Urological Society of Australia and New Zealand (USANZ) and the Royal College of Pathologists of Australasia (RCPA), PCFA established an Expert Advisory Panel (EAP) to review and update the National Health and Medical Research Council (NHMRC) approved 2016 *Clinical practice guidelines for Prostate Specific Antigen (PSA) Testing and Early Management of Test-detected Prostate Cancer* ('2016 Guidelines' accessible via this link 2016 Guidelines). The EAP was made up of relevant multidisciplinary experts and consumers with lived experience of prostate cancer.

Subject specific Working Groups (WG) led by an EAP member were assembled to bring in expertise relevant to the clinical question being investigated. An Aboriginal and Torres Strait Islander advisory group and a men of Sub-Saharan African descent advisory group were assembled to address the unique needs of these populations in Australia.

A Project Steering Committee (PSC) was appointed and charged with responsibility for the overall management and strategic leadership of the guidelines development process. The PSC ensured that all deliverables agreed in the project plan were delivered to acceptable standards in accordance with NHMRC requirements.

A Technical Team (TT) based at the Daffodil Centre Australia conducted the systematic reviews, comprising of systematic literature searches, literature screening against pre-determined inclusion and exclusion criteria and critical evaluation and data extraction of the included literature. The project team was responsible for liaising with the EAP members in regard to content development and content review and working with the PCFA writing team to compile the guidelines document and this technical report.

See the Administrative Report and Appendix 1 of the 2025 Guidelines for information about the governance structure and group membership. Information on how conflicts of interest were managed can be found in the Administrative Report.

2.2 Methods

These Guidelines have been developed following the NHMRC Guidelines Handbook National Health and Medical Research Council [1] and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) evidence to decision processes[2-4] so as to align with the 2016 NHMRC Standards for Guidelines[5].

2.1.1 Stepwise process for preparing clinical practice guidelines to GRADE and NHMRC criteria

Table 1 stepwise process followed in the preparation of these guidelines.

1. For each clinical question, structured question/s (PICO/PECO) were developed to address the clinical question.
2. For each PICO or PECO a systematic review was undertaken as follows
    a. Specify inclusion and exclusion criteria
    b. Search for existing relevant guidelines for adoption
    c. Design and conduct systematic literature searches
    d. Screen literature results against pre-defined inclusion and exclusion criteria
    e. Extract data from included studies
    f. Undertake meta-analyses where appropriate and possible
    g. Conduct risk of bias assessments
    h. Assess certainty of the evidence
    i. Present summary of results and assessments in summary of findings tables
3. Assess the body of evidence and formulate recommendations
4. Write the content narrative

2.2.2 Clinical questions and PICO/PECO questions

Clinical questions were developed by the WGs and EAP following review of the 2016 Guidelines, consideration of advances in technology and current clinical care for the early detection of prostate cancer. To address each clinical question the TT and WG developed one or more questions structured according to the populations, interventions, comparisons, outcomes of interest (PICO) or populations, exposures, comparisons, outcomes of interest (PECO). Each PICO or PECO question was addressed by a systematic review. In some instances, the PICO or PECO was a modification of a PICO or PECO used for the 2016 guidelines and the systematic review was an update of a 2016 guidelines systematic review. The below table lists the clinical questions and PICO or PECO questions for each topic.

Table 2 Clinical questions and PICO or PECO questions for the 2025 Guidelines

Clinical Question (CQ)	PICO or PECO
CQ 1 What is the risk of diagnosis of clinically significant prostate cancer or prostate cancer-specific mortality associated with family histories of prostate cancer overall and by age groups?	**PECO 1** For asymptomatic individuals, what is the risk of being diagnosed with clinically significant prostate cancer or prostate cancer-specific mortality overall and at different ages associated with family histories of prostate cancer based on the age at diagnosis, number and relatedness of relatives with prostate cancer or who died of prostate cancer when compared to individuals who do not have a family history of prostate cancer?
CQ2 What is the risk of diagnosis of clinically significant prostate cancer or prostate cancer-specific mortality for those of sub-Saharan ancestry compared with the risks for the those of other ancestries, overall and by age groups?	**PECO 2** For asymptomatic individuals in Australia, what is the risk of being diagnosed with clinically significant prostate cancer or prostate cancer-specific mortality, overall and by age group, for individuals of sub-Saharan ancestry when compared to individuals of other ancestries?
CQ 3 What is the risk of diagnosis of clinically significant prostate cancer or prostate cancer-specific mortality for those who identify as Aboriginal and Torres Strait Islander peoples compared with the risk for the those who do not, overall and by age groups?	**PECO 3** For asymptomatic individuals in Australia, what is the risk of being diagnosed with clinically significant prostate cancer or prostate cancer-specific mortality overall and by age group for those who identify as Aboriginal or Torres Strait Islander peoples when compared to individuals who do not identify as Aboriginal or Torres Strait Islander peoples?
CQ 4 How best can digital rectal examination (DRE) be used, if at all, in association with prostate specific antigen (PSA) testing in the primary care setting?	**PICO 4** For individuals at risk of prostate cancer without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what is the incremental value of performing a DRE in addition to PSA testing in detecting clinically significant cancer?

Clinical Question (CQ)	PICO or PECO
CQ 5 For males with no history or symptoms of prostate cancer, who are not at higher risk of clinically significant prostate cancer or prostate cancer mortality: At what age should PSA testing commence? How often should PSA testing occur? When should PSA testing cease? What PSA level should be used as a threshold to take further action/investigation?	**PICO 5** For individuals without a prostate cancer diagnosis or symptoms that might indicate prostate cancer and are not at higher risk of either clinically significant prostate cancer or of prostate cancer mortality what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality, all-cause mortality, or the incidence of metastases at diagnosis or on follow-up?
CQ 6 For males with no history or symptoms of prostate cancer who are athigher risk of clinically significant prostate cancer or prostate cancer mortality: At what age should PSA testing commence? How often should PSA testing occur? When should PSA testing cease? What PSA level should be used as a threshold to take further action/investigation?	**PICO 6** For individuals without a prostate cancer diagnosis or symptoms that might indicate prostate cancer who are at higher risk of clinically significant prostate cancer or of prostate cancer mortality what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality, all-cause mortality, or the incidence of metastases at diagnosis or on follow-up?

Clinical Question (CQ)	PICO or PECO
CQ 7 Can/should we use mpMRI to triage men with no history of prostate cancer and an elevated PSA for biopsy?	**PICO 7A** For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, how does mpMRI triage for biopsy compare with all individuals undergoing biopsy for diagnostic accuracy outcomes? **PICO 7B (7Ba and 7Bb)** **7Ba** For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, how does mpMRI triage for biopsy compare with all individuals undergoing biopsy for the outcomes of all-cause mortality, prostate cancer mortality, metastatic disease and the detection of clinically significant cancer in randomised controlled trials? **7Bb** For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, and who are mpMRI negative and do not undergo biopsy how do different follow-up protocols compare for the outcomes of all-cause mortality, prostate cancer mortality and metastatic disease? **PICO 7C (7Ca and 7Cb)** **7Ca** For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, how does triage using mpMRI with or without PSA density using a threshold of 0.15 µg/L/mL compare with triage using mpMRI alone and with all individuals undergoing biopsy for diagnostic accuracy outcomes? **7Cb** For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, how does triage using mpMRI with or without PSA density using a threshold of 0.15 or 0.20 µg/L/mL compare with triage using mpMRI alone and with all individuals undergoing biopsy for diagnostic accuracy outcomes?

Clinical Question (CQ)	PICO or PECO
CQ 8 For biopsy naïve men with a PI-RADS 4 or 5 lesion on mpMRI are targeted biopsies alone acceptable/reasonable/adequate?	**PICO 8A** For biopsy naïve men with a PI-RADS 4 or 5 lesion on mpMRI how do the rates of clinically significant and insignificant cancers detected using a targeted biopsy alone compare with those using a targeted biopsy together with a 20 or more-core systematic biopsy? **PICO 8B (if targeted biopsy alone not considered acceptable/reasonable/adequate)** For biopsy naïve men with a PI-RADS 4 or 5 lesion on mpMRI how do the rates of clinically significant and insignificant cancers detected using a targeted biopsy together with a 12-core systematic biopsy compare with those using a targeted biopsy together with a 20 or more-core systematic biopsy? **PICO 8C (8Ca and 8Cb)** **8Ca** For men undergoing a MRI targeted biopsy, does eliminating a systematic biopsy reduce biopsy complications? **8Cb** For men undergoing a MRI targeted biopsy, does reducing the number of systematic biopsy cores reduce biopsy complications?
CQ 9 For biopsy naïve men with a PI-RADS 3 lesion on mpMRI are targeted biopsies alone acceptable/reasonable/adequate?	**PICO 9A** For biopsy naïve men with a PI-RADS 3 lesion on mpMRI how do the rates of clinically significant and insignificant cancers detected using a targeted biopsy alone compare with those using a targeted biopsy together with a 20 or more-core systematic biopsy? **PICO 9B (if targeted biopsy alone not considered acceptable/reasonable/adequate)** For biopsy naïve men with a PI-RADS 3 lesion on mpMRI how do the rates of clinically significant and insignificant cancers detected using a targeted biopsy together with a 12-core systematic biopsy compare with those using a targeted biopsy together with a 20 or more-core systematic biopsy? **PICO 9C** **9Ca** For men undergoing a MRI targeted biopsy, does eliminating a systematic biopsy reduce biopsy complications? **9Cb** For men undergoing a MRI targeted biopsy, does reducing the number of systematic biopsy cores reduce biopsy complications?

Clinical Question (CQ)	PICO or PECO
CQ 10 What should be the criteria for choosing active surveillance in preference to definitive treatment to offer as primary management to individuals who have a positive prostate biopsy?	**PICO 10A and 10A (subgroups)** For individuals with biopsy-diagnosed localised prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than immediate prostatectomy? **PICO 10B and 10B (subgroups)** For individuals with biopsy-diagnosed localised prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than immediate radiotherapy?
CQ 11 What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?	**PICO 11A** For individuals with biopsy-diagnosed localised prostate cancer, which active surveillance protocols achieve equivalent or better outcomes in terms of length and quality of life than immediate prostatectomy? **PICO 11B** For individuals with biopsy-diagnosed localised prostate cancer, which active surveillance protocols achieve equivalent or better outcomes in terms of length and quality of life than immediate radiotherapy? **PICO 11C** For individuals with biopsy-diagnosed localised prostate cancer following an active surveillance protocol, which combination of monitoring tests, testing frequency and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?

2.2.3 Systematic review process

2.2.3.1 Guideline searches

For each PICO/PECO question, a search for relevant guidelines was conducted by scanning the citations identified by the literature searches (see 2.2.3.2 below) and by searching various websites and databases. (see Systematic review reports).

To be considered for adoption by the WG, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards[5], i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations. Relevant guidelines that did not meet the criteria for adoption were checked for systematic reviews that could be used as a source of relevant references to inform the systematic review process for the PICO/PECO question.

2.2.3.2 Developing selection criteria and systematic search strategies

For each PICO/PECO question, inclusion and exclusion criteria were specified by the TT in consultation with the WG and systematic literature search strategies were developed by the technical team. For most systematic reviews the literature was first searched for recent systematic reviews that were considered to cover the literature up to a certain date. Articles included in such reviews were assessed for inclusion. Searches for original articles were then undertaken to identify for more recent potentially relevant articles or, in the absence of a systematic review covering the recent relevant literature, any potentially relevant articles. Searches for original articles were designed by combining text words and MESH and subject terms where appropriate. The Medline, Embase and Cochrane Database of Systematic Reviews databases were searched for all questions. For PICOs restricted to randomised controlled trials the Cochrane Central Register of Controlled Trials was searched. All searches were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. The full detailed systematic literature search strategy for each PICO/PECO can be found in Systematic review reports.

2.2.3.3 Literature searches

All retrieved literature results were screened against the pre-defined inclusion and exclusion criteria (see Systematic review reports) in two stages.

- **First screen** - the titles and abstracts of articles identified by the literature searches were screened by one or two reviewers. Full texts of potentially relevant articles were collected for further evaluation.
- **Second screen** – the full text of potentially relevant articles identified from the literature searches and any systematic reviews comprehensively covering the earlier literature were against the pre-defined inclusion and exclusion criteria for inclusion by one or two reviewers.

If the systematic review was an update of a systematic review undertaken for the 2016 guidelines the full texts identified by the previous searches for further evaluation were reassessed for inclusion in the current systematic review update. In addition, reference lists of included articles and recent relevant guidelines were checked for potential additional articles and the full texts of these articles were assessed for inclusion. For full details of the search methods used to identify articles for inclusion for each PICO/PECO can be found in Systematic review reports.

2.2.3.4 Data extraction and analyses

Data was extracted from included studies. One reviewer extracted data from the included studies which was then checked by a second reviewer. Data extracted included details of included studies presented in tables of study characteristics, and effect estimates and their 95% confidence intervals for each included outcome presented in tables of results. Pooled analyses were planned where there were two or more studies reporting the same outcome at corresponding time points.

For full details of the data extracted and any meta-analyses undertaken for each PICO/PECO can be found in Systematic review reports.

2.2.3.5 Risk of bias assessments

Two reviewers independently assessed the risk of bias of each of the included studies for each critical outcome using a study design specific assessment tool and where necessary pre-specified criteria. Any disagreements were adjudicated by a third reviewer. For full details of the risk of bias assessment methods for each PICO/PECO can be found in the Systematic review reports.

2.2.3.6 GRADE assessment of the certainty of evidence

A GRADE approach was used to assess the certainty of the body of evidence for each critical outcome for each PICO/PECO[5]. The certainty of the body of evidence for each critical outcome was rated high, moderate, low or very low based on assessment of the risk of bias, indirectness of the results, imprecision, inconsistency or heterogeneity of the results and publication bias following GRADE guidance.[2,6-10]

Imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. These thresholds were determined by the clinical Working Group and following GRADE guidance provided by Schunemann 2022.[8] See Minimal clinically important differences for more information on MCIDs and a list of MCIDs used in this guideline.

The outcomes of the GRADE assessment can be found in the Systematic review report for each PICO/PECO.

2.2.3.7 Minimal clinically important differences

A minimal clinically important difference (MCID) is the smallest change in disease outcome that a patient would consider beneficial and that would result in a change in how the disease is managed. MCIDs were used throughout these Guidelines to interpret the data extracted from the systematic review and to determine the clinical significance of an observed effect. MCIDs were determined before analyses were undertaken.

MCIDs for continuous patient reported outcomes were calculated based on methods published for individuals diagnosed with localised prostate cancer[11-13] and advice from experts.

There are no published MCIDs for dichotomous prostate cancer outcomes. MCIDs for these outcomes were developed following GRADE guidance[2] by the MCID Working Group with support from the MRI, DRE and prostate biopsy working groups. The MCID working group included a consumer, a general practitioner, a urology nurse practitioner a methodologist, an epidemiologist and clinical specialists. More information on working groups can be found in the Administrative report and Appendix 1 of the 2025 Guidelines.

For dichotomous outcomes MCIDs were determined for each outcome or event and are expressed as the minimal difference in the number of individuals with the outcome in a total of 1000 or 10,000 individuals considered clinically significant.

For example, if an MCID for an outcome is 100/1000 and 110 more individuals in the intervention group had this outcome in a population of 1000, the effect of the intervention was considered

clinically significant. However, if 90 more individuals in the intervention group had the outcome in a population of 1000, the effect of the intervention was considered clinically insignificant.

The table below shows the rankings and MCIDs for various prostate cancer health states and outcomes considered in these Guidelines. Rankings and MCIDs were based on reported utilities. Where utilities were not available for a specific event or outcome, their ranking and MCID was determined by the MCID WG in consultation with, MRI, biopsy and DRE working groups. Contemporary reports of patients' preferences and consumer advice and input was extensively used in this process. The MCID working group agreed that the threshold for a moderate effect would be double the MCID and the threshold for a large effect would be four times the MCID for all outcomes.

Table 3: Minimal clinically important differences (MCIDs) for dichotomous outcomes based on ranking of health states or outcomes used for these Guidelines

Rank	Health state or event (outcome)	Basis for ranking	MCID
1	Perfect health	U	Not applicable
2	PSA test	G	Not required for these Guidelines
3	Abnormal PSA or DRE test – Further unnecessary tests	M	> 100 per 1000
4	MRI	G	Not required for these Guidelines
5	Biopsy	U	100 per 1000
5	Undetected ISUP grade 1 with close follow-up for those who are not biopsied	M	100 per 1000
6	Post biopsy infection	U	Not required for these Guidelines
7	Hospitalisation within 30 days of biopsy	M	50 per 1000
8	Undetected ISUP grade ≥ grade 2 with close follow-up for those who are not biopsied or who undergo targeted biopsy only and the biopsy is negative	M	50 per 1000
9	Undetected ISUP grade ≥ grade 3 with close follow-up for those who are not biopsied	M	35 per 1000
10	Metastatic/advanced disease/ palliative therapy at 15 years follow-up	U, M	30 per 1000 – patients with localised prostate cancer 30 per 10000 individuals screened
11	End of life	U	Not required for these Guidelines
12	Death at 15 years follow-up	U, M	15 per 1000 – patients with localised prostate cancer 15 per 10000 individuals screened

Legend for basis for rankings

(U) Utilities rankings – a health-related quality of life measure that assign a value to different health states, ranging from 0 (death) to 1 (perfect health).

(M) Rankings for additional outcomes determined by the MRI, DRE, biopsy and MCID Working Groups

(G) Godtman 2024[14] which reports patients' preferences with respect to MRIs and biopsies

2.2.3.8 Summary of findings tables

For each PICO/PECO, the summary of finding tables present for each critical outcome, the GRADE certainty of evidence, the effect estimate, the risks in the control groups and the intervention or exposed groups and the absolute difference between the control and intervention or exposed groups where calculable. Risks in the intervention or exposed group and the absolute difference between the control and intervention arms were estimated following GRADE guidance outlined in the GRADE Handbook. The magnitude of the absolute difference was determined using thresholds for small, moderate and large absolute effects thresholds based on the MCIDs as determined by the MCID WG.

2.2.3.9 Evidence to decision process

Clinical recommendations were developed, and the strength of evidence-based recommendations determined for each clinical question using the summary of findings table and the GRADE evidence to decision framework.[2,3,15]

The GRADE evidence to decision framework was used to capture the body of available evidence, supporting evidence outside the scope of the systematic review and expert opinion into a single Evidence to Decision (EtD) table for each clinical question. The body of evidence may include evidence from more than one systematic review. Each EtD table includes an assessment of the following items:

- The **size** of the **benefits/desirable effects**
- The **size** of the **harms/undesirable effects**
- The **balance** between **benefits/desirable effects** and **harms/undesirable effects**.
- **Certainty of evidence**: confidence in the estimates of effect (quality of evidence).
- **Values and preferences**: variability in how people or patients in the population of interest value the different outcomes.
- **Acceptability**: is the recommendation acceptable to people or patients in the population of interest, their care-givers and their health providers
- **Feasibility**: are there barriers that could limit the implementation of the recommendation.

The items included for assessment were based on NHMRC and GRADE guidance.[2,3,4,15,16] An individual perspective was used as the guidelines are intended for health practitioners.

For each clinical question, EtD table content can be found in the relevant evidence to decision section of the 2025 guidelines. For each table, information regarding assessment of the size of the desirable and undesirable effects and balance between the desirable and undesirable effects are included in the "harms and benefits" section and assessments of acceptability and feasibility are included in the "Resources and other considerations" section.

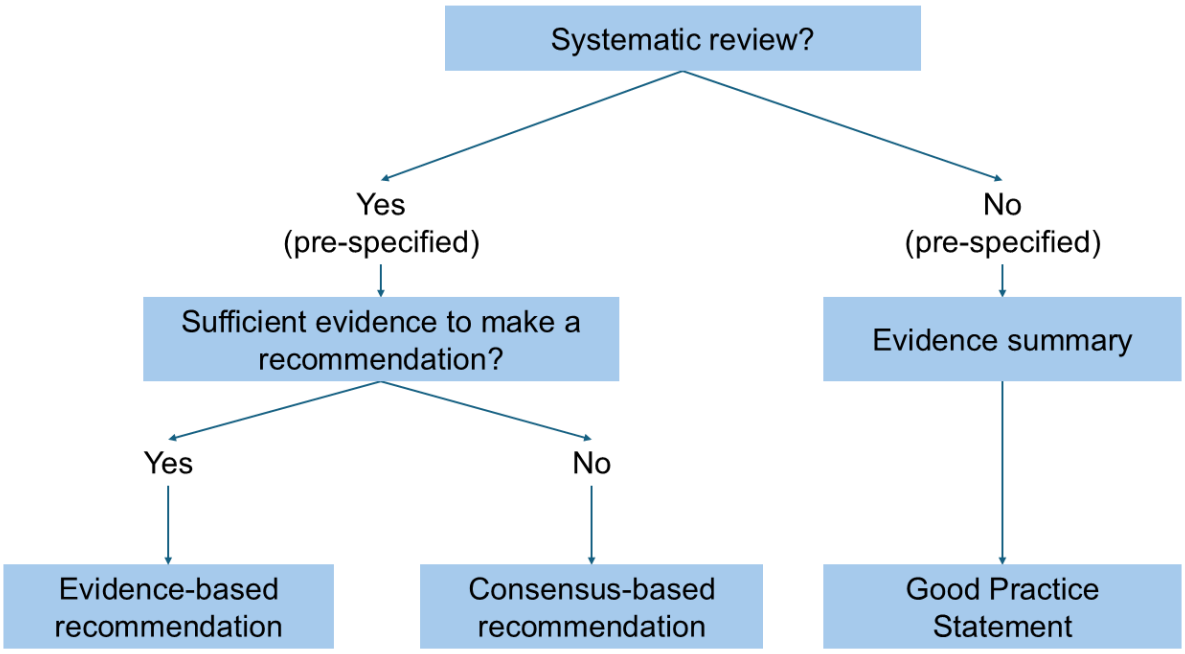
2.2.3.10 Types of recommendations

Following guidance provided by the NHMRC Guidelines for Guidelines Handbook[1] and Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines May 2011 version 1.1.[17]

Three main types of recommendations were used in these Guidelines:

- Evidence–based – a recommendation based on the best available evidence from one or more systematic reviews.
- Consensus-based – a recommendation based on expert opinion and consumer input using a consensus process, after a systematic review of the evidence found insufficient evidence on which to base an evidence-based recommendation.
- Good practice statement – known also as a practice point, these are points of guidance included in these Guidelines to support evidence-based recommendations, where the subject matter is outside the scope of the PICOs for the clinical questions. These recommendations are formulated based on expert opinion and consumer input using a consensus process.

The flowchart below provides an overview of how the recommendations were developed.



2.2.3.11 Strength of evidence-based recommendations

GRADE uses two categories for the strength of recommendations:

Strong recommendations; or
Conditional recommendations.

Strong and conditional recommendations can be for or against an intervention. The table 4. below defines the different types of recommendations.

Table 4 Definitions of the different types of recommendations

Recommendation strength	Criteria
Strong recomendation Benefits likely outweigh harms for almost everyone. All or nearly all informed patients would likely want this option	**Evidence-based recommendation** High/moderate quality of evidence The desirable effects of the proposed intervention clearly outweigh its undesirable effects, and Most or all individuals will be best served by the recommended course of action, and Most or all informed individuals would **want the intervention**. **Patients** • **most or all individuals** in this situation would want the recommended course of action and only a small proportion would not **Clinicians** • **most** patients **should** receive the recommended course of action
Strong recommendation against Harms likely outweigh benefits for almost everyone. All or nearly all informed patients would likely not want this option	**Evidence-based recommendation** High/moderate quality of evidence The undesirable effects of the proposed intervention clearly outweigh its desirable effects, and Most or all individuals will be best served by the recommended course of action, and Most or all informed individuals would **not want the intervention**. **Patients** • **most or all individuals** in this situation would not want the recommended course of action and only a small proportion would **Clinicians** • **most** patients should receive the recommended course of action

Conditional recomendation Benefits may outweigh harms for the majority, but not for everyone.	**Evidence-based recommendation** Close balance between the desirable and undesirable effects Low or very low certainty as to the magnitude of desirable and/or undesirable effect, or Uncertainty or important variability in the value patients place on the treatment outcomes, or Important issues with acceptability and feasibility of proposed intervention for patients, caregivers or health professionals **Patients** **the majority** of individuals in this situation would want the recommended course of action but **many would not** **Clinicians** Recognise that different choices will be appropriate for different patients, and **that you must help each patient arrive at a management decision** consistent with their values and preferences. **Need to allocate more time to shared decision making**, making sure that they clearly and comprehensively explain the potential benefits and harms to a patient.
Conditional recommendation against Harms may outweigh benefits for the majority, but not for everyone. The majority of patients would likely not want this option	**Evidence-based recommendation** Close balance between the desirable and undesirable effects but the undesirable effects of the proposed intervention probably outweigh its desirable effects, or Uncertainty as to the magnitude of desirable and/or undesirable effects, or Uncertainty or important variability in the value patients place on the treatment outcomes, or Important issues with acceptability and feasibility of proposed intervention for patients, caregivers or health professionals **Patients** the **majority** of individuals in this situation would not want the recommended course of action but **some would** **Clinicians** Recognise that different choices will be appropriate for different patients, and **that you must help each patient arrive at a management decision** consistent with their values and preferences. **Need to allocate more time to shared decision making**, making sure that they clearly and comprehensively explain the potential benefits and harms to a patient.
Consensus recommendation	A recommendation based on expert opinion and consumer input formulated using a consensus process, after a systematic review of the evidence was undertaken and found insufficient evidence on which to base a recommendation.

Good practice statement	Points of guidance included in these Guidelines used to support evidence-based recommendations, where the subject matter is outside of the scope of the PICOs for the clinical question, and which were formulated based on expert opinion and consumer input using a consensus process.

2.2.3.12 Drafting the clinical recommendations

For each clinical question, the relevant subject working group drafted clinical recommendations based on the results of their assessments of the harms and benefits, the certainty of the evidence, men's values and preferences, and the acceptability and feasibility in regard to the proposed recommendation. All recommendations were approved by the EAP and the PSC

2.2.3.13 Writing the guideline content

For each clinical question the guideline chapter was drafted based on the requirements of MAGICapp. Sections include:

- **Clinical question**
- **Background**
- **Recommendations:** the clinical recommendation, it's direction (for or against) and its strength (Strong, Conditional, Consensus or Good practice statement).
- **Evidence to decision**: Assessments of the harms and benefits, the certainty of the evidence, men's values and preferences, and the acceptability and feasibility in regard to the proposed recommendation.
- **Rationale:** Description of the basis for the recommendation based on the the evidence to decision assessments.
- **Evidence:** Includes PICOs/PECOs, summary of evidence from systematic review including certainty of evidence and detailed evidence tables
- **References**: Reference list for the section.

2.3 NHMRC Evidence Statement Forms

For these guidelines GRADE evidence to decision frameworks (sections 2.2.3.9 and 2.2.3.12) were used to develop evidence based recommendations instead of NHMRC Evidence Statement Forms.

2.4 References

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3 Systematic Review Reports

3.1 Clinical Question 1 – Family History

Clinical question: *What is the risk of diagnosis of clinically significant prostate cancer or prostate cancer-specific mortality associated with family histories of prostate cancer overall and by age groups?*

Systematic review report on the relative risks of clinically significant prostate cancer or prostate cancer-specific mortality for individuals with family histories of prostate cancer

Authors

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Introduction

This review is an update of the previous systematic review undertaken for the 2016 guidelines. Since 2016 clinical interest has shifted from any prostate cancer to clinically significant prostate cancer to reduce harms associated with overdiagnosis. To ensure clinical relevancy, for this update, the outcome of diagnosis of any prostate cancer was replaced by diagnosis of clinically significant prostate cancer.

PECO

This systematic review addresses the following PECO which is summarised in detail in Table 1.
For asymptomatic individuals, what is the risk of being diagnosed with clinically significant prostate cancer or prostate cancer-specific mortality overall and at different ages associated with family histories of prostate cancer based on the age at diagnosis, number and relatedness of relatives with prostate cancer or who died of prostate cancer when compared to individuals who do not have a family history of prostate cancer?

Table 1. *PECO components*

Population	*Exposure*	*Comparator*	*Outcomes*	*Study design*
Individuals at risk of prostate cancer without a prostate cancer diagnosis or symptoms that might indicate prostate cancer	Family history of prostate cancer: By age at diagnosis, number, and relatedness of relatives with a diagnosis of prostate cancer or who died of prostate cancer	No known family history of prostate cancer or General population	Prostate cancer mortality or Clinically significant prostate cancer diagnosis • Overall • By age group	Cohort or Nested case-control or Systematic reviews thereof

1. Methods

1.1 Selection Criteria

Table 2. *Selection criteria for systematic review of the relative risks of clinically significant prostate cancer and prostate cancer mortality for individuals with a family history of prostate cancer*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Aetiology /risk factor	
Study design	Cohort studies (prospective or retrospective) Nested case-control studies Systematic reviews of above	Case-control studies Non-systematic reviews
Population	People at risk of prostate cancer without a personal history of prostate cancer or symptoms that might indicate prostate cancer	High risk populations e.g. African Americans Population subgroups other than specific age groups e.g. restricted to smokers or those with a pre-existing health condition Populations undergoing screening
Exposure	Independently confirmed family history of prostate cancer including first-degree relative, second-degree relative, brother or father diagnosed with prostate cancer • Overall • By age at diagnosis, number and relatedness of relatives with a diagnosis of prostate cancer or who died of prostate cancer	Did not specify degree of family history i.e. only examined 'family history' Self-reported family history Third degree relatives only
Comparator/ Reference group	People with no known family history of prostate cancer including no first-degree relative diagnosed with prostate cancer General population	Known genetic abnormalities
Outcomes	Clinically significant prostate cancer diagnosis/incidence or Prostate cancer mortality • Overall • By age	Any prostate cancer Prostate cancer survival Metastatic disease
Analyses	Considers age in analyses	
Language	English	
Publication period	2014 onwards (for update) 1990 - 2014 (original 2016 systematic review)	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data

1.2 Definitions and terminology

For the purposes of this review:

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

First degree relatives refers to father, brothers or sons

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).

Second degree relatives refers to grandfathers, uncles, nephews or half-brothers

Third-degree relatives includes first cousin, great-grandparent, great-uncle, great-nephew or half-uncle.

1.3 Guidelines searches

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- *Urological Society of Australia and New Zealand (USANZ) website*

- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

For the 2016 guidelines systematic review searches were undertaken to identify relevant systematic reviews to be used as a means of identifying potentially relevant articles. Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases from 1990 up until 1st March 2014 were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with prostate cancer. For the Medline and Embase databases, family history search terms and a meta-analysis/systematic review filter were added to the prostate cancer search.

To identify recently published relevant articles that may not have been included in systematic reviews, the Medline and Embase searches were run without the meta-analysis/systematic review filter from 1st January 2010. This date was chosen as a recent and comprehensive meta-analysis was identified with a literature search cut-off in 2010. Monthly alerts were run for both Medline and Embase searches until July 2014. To identify studies which considered Aboriginal and Torres Strait Islander peoples, these searches were then coupled with search terms for Aboriginal and Torres Strait Islander peoples and the databases searched from 1990 until 1st March 2014. A complete list of the terms used for all search strategies are included as Appendix A.1. Reference lists of all relevant articles were checked for potential additional articles. The full texts identified by these searches for further evaluation were reassessed for inclusion in the current systematic review update.

To find evidence published from 2014 onwards the Cochrane Database of Systematic Reviews was searched on 13th March 2024 using the term “prostate” and searches were undertaken to identify recent systematic reviews of risks associated with family histories of prostate cancer and relevant original articles. Medline and Embase databases were searched on the 18th December 2024 by combining text words and subject headings for prostate cancer and family history, and in the case of the systematic review search, terms for systematic reviews. These searches were limited to articles published in English from 1st January 2014 onwards. The searches were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the searches are included in Appendix A.2. Titles and abstracts were screened by one reviewer. Full texts of potentially relevant articles were retrieved and were assessed independently by

two reviewers. Differences were resolved by discussion. Reference lists of recent relevant guidelines and full texts retrieved for further assessment were checked for potential additional articles.

1.5 Data extraction and analyses

One reviewer extracted the relevant data from the included studies. A second reviewer checked the extracted data. The following characteristics of the included studies were extracted: population size, age and geographical location, study period, databases used, different family histories, comparator population, relevant outcomes reported and subgroup data available, and details that might inform risk of bias assessments e.g. confounders considered in analyses. The numbers of those exposed and not exposed, the number of events for the exposed and not exposed, and effect estimates and their 95% confidence intervals (95% CIs) were extracted. Subgroup analyses were planned for age groups if available.

To determine absolute differences in risk, we required estimates of risks for the control populations (non-exposed or the general population). For cohort studies these estimates need to be for comparable age groups and take into account length of follow-up. If appropriate estimates of risks in the control populations are not reported, it would not be possible to calculate differences in absolute risk, or the impact of a specific risk in a specific population. In the absence of appropriate estimates of the control group risk, the analyses focussed on identifying which men were at high or higher risk. Following the approaches used in recent international prostate cancer early detection guidelines (Wei 2023; Garraway 2024), men were considered to be at high or higher risk if they had at least double the risk of clinically significant disease or prostate cancer mortality when compared with the general population or non-exposed men. Meta-analyses were planned where appropriate and possible. Meta-analyses were not undertaken where they would require two or more approximations.

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias for each included study with differences resolved by discussion using the ROBINS-E tool (ROBINS-E Development Group 2023). The overall risk of bias of studies was rated low except for concerns about uncontrolled confounding (as studies are observational, the possibility of uncontrolled confounding cannot be eliminated), some concerns, high or very high based on assessments of the risk of bias associated with the following sources of bias: confounding, measurement of exposure, participant selection, post-exposure interventions, missing data, measurement of the outcome, and selection of the reported results. Prespecified important confounders were age, geography (remoteness), socioeconomic status/education and period. Differences in PSA testing behaviours were considered as a source of bias due to post-exposure interventions.

1.7 GRADE assessment of the certainty of the evidence

A GRADE (grading of recommendation, assessment, development and evaluation) approach was used to assess the certainty of the body of evidence for the outcomes of prostate cancer mortality and

clinically significant prostate cancer (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).
The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness of the results, imprecision, inconsistency of the results, and publication bias based on guidance for assessing narrative syntheses provided by Murad 2017 and prognostic studies provided by Foroutan 2020 with additional guidance for the assessment of imprecision provided by Schunemann 2022. Imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. These thresholds were determined by the MCID Working Group, a reference group consisting of a consumer, a general practitioner, a urology nurse practitioner and clinical specialists, following GRADE guidance provided by Schunemann 2022. MCIDs for prostate cancer mortality were dependent on length of follow-up. Where the length of follow-up was not reported and MCIDs could not be determined, imprecision was determined in the context of whether the exposure resulted in a high or higher risk i.e. double the risk by consideration of the effect estimate and whether its 95% confidence interval crossed the threshold for high or higher relative risk, 2.0. Where there was only one study inconsistency could not be rated. Where there were less than 10 studies, publication bias was assessed based on a consideration of potential conflicts of interest.
As per GRADE guidance for prognostic studies (Foroutan 2020), studies started with a high level of certainty in the evidence and were downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.
Definitions of the GRADE ratings of certainty are presented in Appendix B.

2. Results

2.1 Guidelines searches

Three potentially relevant guidelines were identified which were reportedly based on systematic reviews. They were not considered for adoption as for all three guidelines the systematic reviews of the evidence were not accessible. (Appendix C).

2.2 Literature searches

A total of 5 articles reporting on 2 data-linkage cohort studies were included in this systematic review. Figure 1 outlines the process for identifying relevant articles published from 1990 onwards. An appraisal of the 63 full texts considered for the 2016 guidelines identified three articles for inclusion. For the literature searches for the 2025 guidelines update, no relevant systematic reviews published after 2013 were identified. The Medline and Embase database searches retrieved 8501 unique citations which were assessed by one reviewer, of which 66 articles were retrieved for a more detailed evaluation by two reviewers. One additional article was identified for full text evaluation from reference lists of recent relevant guidelines and full texts retrieved for further assessment. Of the 67 articles evaluated for inclusion two met the inclusion criteria. There were no studies that included Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.

The retrieved articles that were not included in this review and the reasons for their exclusion are documented in Appendices D and E. The main reasons for exclusion were no relevant exposures or outcomes, and excluded publication type.

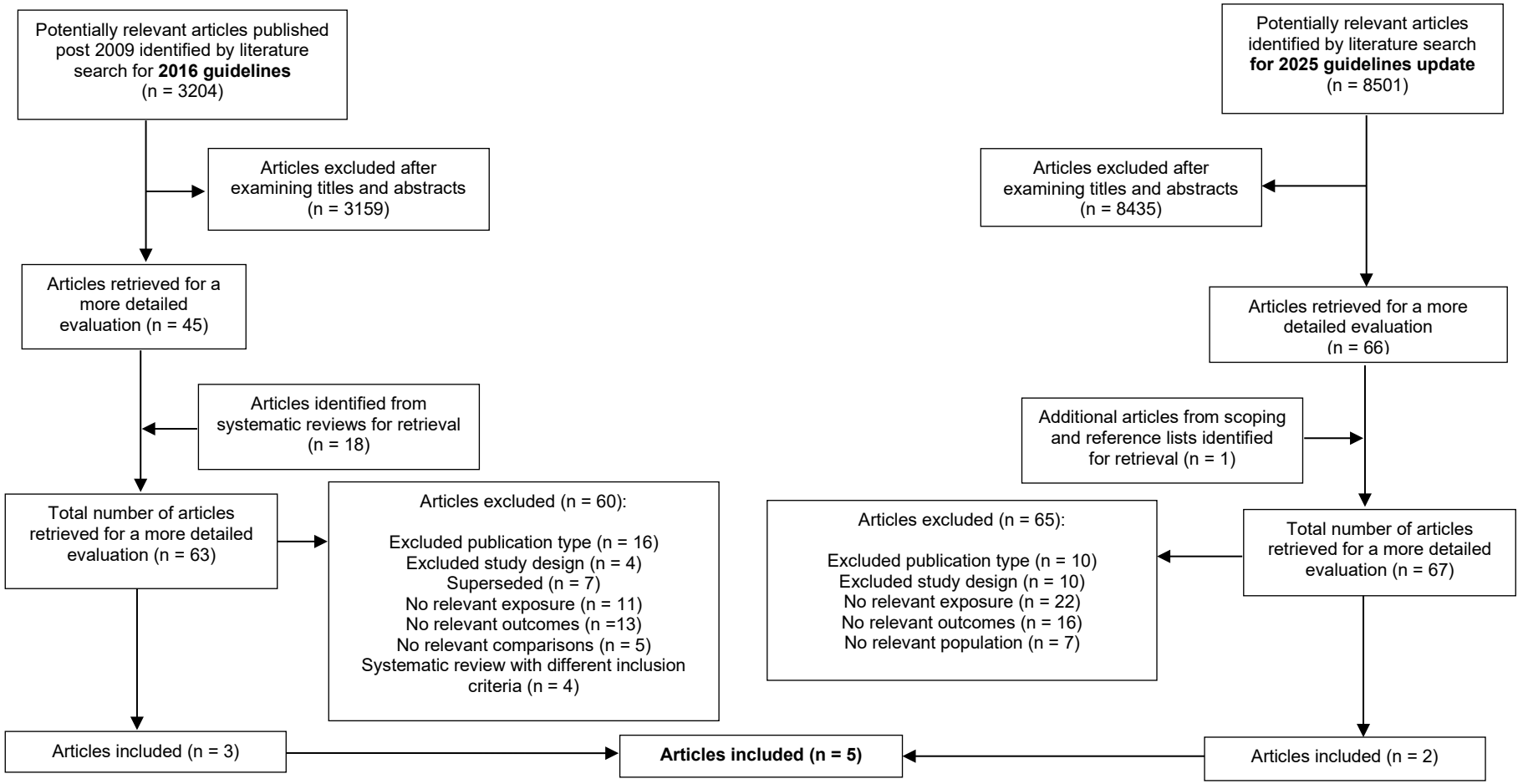

Figure 1. *Process of inclusion and exclusion of articles published from previous and updated systematic reviews*

2.3 Characteristics of included data and study

The characteristics of studies included in the systematic review update are described in **Table 3**.

Table 3. *Characteristics of studies reporting relative risks of clinically significant prostate cancer and prostate cancer mortality for individuals with different family histories of prostate cancer*

Study	***Population***	***Databases (Study period)***	***Exposures***	***Comparator***	***Outcome/s***	***Comments***
Albright 2017, Beebe-Dimmer 2020 (Utah, USA) Retrospective cohort (data linkage) study	Males recorded in the Utah Population Database (UPDB) with at least 12 immediate ancestors (2 parents, 4 grandparents and at least 6 grandparents) N = 686,203 Age: NR Family history of fatal prostate cancer: 29%	Utah Population Database which links records of genealogies of Utah pioneers and their descendants, with information from death certificates from the Utah Department of Health and the Utah Cancer Registry (a National Cancer Institute Surveillance, Epidemiology and End Results registry) and other statewide medical and demographic databases. (1966-2011)	*Family history of **fatal** prostate cancer* Multiple different exposures based on number and degree of relatedness of affected family members Including the following constellations of relatives who died of prostate cancer: 1 FDR (N = 19,022) Father (N = 6694) 1 brother (N = 10,968) 2 brothers (N = 670) 2 FDRs (N = 951) 3 FDRs (N = 94) ≥ 1 FDR (N = 20,076) ≥ 1 FDR aged 50-59 at death (N = 1304) ≥ 1 FDR aged 60-69 at death (N = 5463) ≥ 1 FDR aged 70-79 at death (N = 8154) ≥ 2 FDRs (N = 1054) ≥ 3 FDRs (N = 103) 0 FDR + ≥ 1 SDR (N = 51,934) 0 FDR + ≥ 1 SDR aged 50-59 at death (N = 3688) 0 FDR + ≥ 1 SDR aged 60-69 at death (N = 14,720) 0 FDR + ≥ 1 SDR aged 70-79 at death (N = 20,768) 0 FDR + ≥ 2 SDRs (N = 5209) 0 FDR + ≥ 3 SDRs (N = 506) 0 FDR or SDR + ≥ 1 TDR	No family history of fatal prostate cancer No FDRs, SDRs or TDRs with a record of fatal prostate cancer N = 489,960	Prostate cancer mortality Maximum follow-up= 45 years	Prostate cancer mortality defined as a prostate cancer diagnosis recorded in Utah Cancer Registry and prostate cancer recorded as a cause of death on a Utah death certificate Calculated expected number of events for 5-year birth and birth state cohorts Censored those with cancer diagnosis prior to 1966, prostate cancer deaths or diagnoses outside of Utah, prostate cancer cases still living and whose status for prostate cancer death remains unknown, and prostate cancer diagnosis after 2011

			(N = 124,233) 0 FDR or SDR + ≥ 2 TDRs (N = 24,116) 0 FDR or SDR + ≥ 3 TDRs (N = 5427) 1 FDR + ≥ 1 SDR (N = 3180) 1 FDR + ≥ 2 SDRs (N = 551) 1 FDR + ≥ 3 SDRs (N = 70)			
	Males recorded in the Utah Population Database (UPDB) and are members of a pedigree with at least 3 consecutive generations resident in Utah during or after 1966 with known birth year and birth state N = 619,630 Age ≥ 40 years % Family history of prostate cancer NR	(1966-2016)	*Family histories of prostate cancer **diagnoses*** ≥ 2 FDRs or SDRs on the same side of the family diagnosed with prostate cancer N = 77,078 (12.4%) ≥ 2 FDRs or SDRs diagnosed with prostate cancer at age ≤ 55 years N = 893 (0.1%) ≥ 3 FDRs diagnosed with prostate cancer N = 2618 (0.4%) ≥ 3 relatives spanning 3 generations with prostate cancer N = 11,104 (1.8%)	< 2 FDRs or SDRs on the same side of the family diagnosed with prostate cancer N = 542,552 < 2 FDRs or SDRs diagnosed with prostate cancer at age ≤ 55 years, or < 3 FDRs diagnosed with prostate cancer, or ≥ 3 relatives spanning 3 generations diagnosed with prostate cancer N = 606,131	Maximum follow-up = 50 years	Prostate cancer mortality recorded as primary cause of death on death certificate or in Utah Cancer Registry Adjusted for 5-year birth groups, birth state and number of male relatives
Brandt 2010, Hemminki 2011, Brandt 2012 (Sweden) Retrospective cohort (data linkage) study	Males born in 1932 or later recorded together with their biological parents in the Swedish – Family Cancer Database living in Sweden N = 3.9 million Maximum age: 74 years % Family history: NR	Swedish Family – Cancer Database which links information from nationwide Swedish Cancer Registry with Multigenerational Register, national censuses, death notifications datasets – 2008 update (1961-2006)	*FDRs **diagnosed** with prostate cancer* Number with exposure NR 1 FDR - Father Father diagnosed aged: 0-59 years 60-64 years 65-74 years 75-82 years > 82 years 1 FDR - One brother Brother diagnosed aged: 0-59 years 60-64 years 65-74 years 2 FDRs - Father + 1 brother	No FDRs diagnosed with prostate cancer N: NR	Prostate cancer mortality Maximum follow-up = 45 years	Swedish Cancer Registry has almost 100% coverage of cancer cases in Sweden Cause of death from Swedish Causes of death Register Censoring events were immigration, 31/12/2006, absence at census and death from a cause other than prostate cancer Age, socioeconomic status, calendar period and region

			2 FDRs - 2 brothers 3 FDRs - Father + 2 brothers 3 FDRs - 3 brothers *FDRs who **died** of prostate cancer* 1 FDR - Father 1 FDR - One brother 2 FDRs - Father + brother			were taken into account in analyses
			1 FDR – Father ***Died** of prostate cancer*	Father not diagnosed with prostate cancer	Prostate cancer mortality Maximum follow-up = 45 years	Censoring events were immigration, 31/12/2006, absence at census and death due to a cause other than prostate cancer Age, socioeconomic status, calendar period and region were taken into account in analyses
	Maximum age: 76 years	2010 update (1961-2008)	*FDR **died** of prostate cancer* 1 FDR - Father ≥ 1 FDR – Brother	Swedish male population	Prostate cancer mortality Maximum follow-up = 47 years	Censoring events were immigration, 31/12/2008, absence at census and death Standardised mortality ratios standardised for age, calendar period, socioeconomic status and region

FDR = first degree relative; N = number; NR = not reported; SDR = second degree relative; TDR = third degree relative

2.4 Results by outcomes of interest

Prostate cancer mortality – results presented in Table 4

Clinically significant prostate cancer – no relevant results found

Table 4. *Results of cohort studies reporting relative risks of prostate cancer mortality associated with different family histories of prostate cancer*

Study	Period at risk (years)*	N	Exposure	N exposed	Comparator	Prostate cancer deaths (N)		Effect estimate (95%CI)
						Exposed	Comparator	
Family history of prostate cancer mortality								
Swedish cohort								
Brandt 2010	0-34	3.9 million	1 FDR – Father	NR	No FDRs diagnosed with prostate cancer N: NR	202	2113	HR[c] = 2.08 (1.80-2.41)
			1 FDR – 1 brother	NR		15	2113	HR[c] = 2.30 (1.38-3.81)
			2 FDRs – Father + 1 brother	NR		4	2113	HR[c] = 6.86 (2.57-18.28)
Hemminki 2011	0-34	3.9 million	1 FDR – Father	NR	Father not diagnosed with prostate cancer N: NR	206	2082	HR[c] = 2.03 (1.76-2.35)
Brandt 2012	0-36	3.9 million	1 FDR – Father	NR	Swedish male population 3.9 million	280	NR	SMR[d] = 2.04 (1.81-2.29)
			≥ 1 FDR – Brother	NR		36	NR	SMR[d] = 2.75 (1.93-3.80)
Utah cohort								
Albright 2017	0 - >40	686,203	0 FDR or SDR + ≥ 1 TDR	124,233	No family history of prostate cancer mortality N = 489,960	1065	1999	RR[a] = 1.32 (1.24-1.40)
			0 FDR or SDR + ≥ 2 TDR	24,116		314	1999	RR[a] = 1.44 (1.29-1.61)
			0 FDR or SDR + ≥ 3 TDR	5427		94	1999	RR[a] = 1.63 (1.32-2.00)
			0 FDR + ≥ 1 SDR	51,934		435	1999	RR[a] = 1.65 (1.50-1.81)
			0 FDR + ≥ 1 SDR earliest relative aged 50-59 at death	3688		26	1999	RR[a] = 1.29 (0.84-1.89)
			0 FDR + ≥ 1 SDR earliest relative aged 60-69 at death	14,720		135	1999	RR[a] = 1.90 (1.59-2.25)
			0 FDR + ≥ 1 SDR earliest relative aged 70-79 at death	20,768		173	1999	RR[a] = 1.70 (1.46-1.98)

			0 FDR + ≥ 2 SDRs	5209		71	1999	RR[a] = 2.54 (1.98-3.20)
			0 FDR + ≥ 3 SDRs	506		11	1999	RR[a] = 4.49 (2.24-8.03)
			1 FDR - Father	6694		61	1999	RR[a] = 1.94 (1.49-2.50)
			1 FDR	19,022		475	1999	RR[a] = 2.49 (2.27-2.73)
			1 FDR - 1 brother	10,968		398	1999	RR[a] = 2.62 (2.37-2.89)
			1 FDR + ≥ 1 SDR	3180		83	1999	RR[a] = 3.18 (2.53-3.94)
			1 FDR + ≥ 2 SDRs	551		20	1999	RR[a] = 4.99 (3.05-7.71)
			1 FDR + ≥ 3 SDRs	70		4	1999	RR[a] = 10.56 (2.88-27.03)
			≥ 1 FDR	20,076		545	1999	RR[a] = 2.67 (2.45-2.91)
			≥ 1 FDR earliest relative aged 50-59 at death	1304		42	1999	RR[a] = 3.63 (2.62-4.91)
			≥ 1 FDR earliest relative aged 60-69 at death	5463		161	1999	RR[a] = 3.09 (2.63-3.61)
			≥ 1 FDR earliest relative aged 70-79 at death	8154		219	1999	RR[a] = 2.57 (2.24-2.94)
			2 FDRs	951		63	1999	RR[a] = 5.15 (3.96-6.59)
			2 brothers	670		45	1999	RR[a] = 4.63 (3.38-6.20)
			≥ 2 FDRs	1054		70	1999	RR[a] = 5.16 (4.03-6.52)
			3 FDRs	94		7	1999	RR[a] = 5.76 (2.32-11.87)
			≥ 3 FDRs	103		7	1999	RR[a] = 5.30 (2.13-10.93)
Family history of prostate cancer								
Swedish cohort								
Brandt 2010	0-34	3.9 million	1 FDR - Father	NR	No FDRs diagnosed with prostate cancer N: NR	306	2113	HR[c] = 1.81 (1.61-2.04)
			1 FDR - Father diagnosed aged 0-59 years	NR		7	2113	HR[c] = 2.06 (0.98-4.32)
			1 FDR - Father diagnosed aged 60-64 years	NR		23	2113	HR[c] = 2.55 (1.69-3.85)
			1 FDR - Father diagnosed aged 65-74 years	NR		105	2113	HR[c] = 1.97 (1.62-2.40)
			1 FDR - Father diagnosed aged 75-82 years	NR		112	2113	HR[c] = 1.67 (1.38-2.10)
			1 FDR - Father diagnosed aged > 82 years	NR		59	2113	HR[c] = 1.63 (1.26-2.12)
			1 FDR - 1 brother	NR		139	2113	HR[c] = 2.75 (2.32-3.26)
			1 FDR -1 brother diagnosed aged 0-59 years	NR		32	2113	HR[c] = 3.27 (2.31-4.64)
			1 FDR -1 brother diagnosed aged 60-64 years	NR		44	2113	HR[c] = 2.55 (1.89-3.44)
			1 FDR -1 brother diagnosed aged 65-74 years	NR		63	2113	HR[c] = 2.67 (2.08-3.43)

			2 FDRs - Father + 1 brother	NR		24	2113	HR[c] = 2.96 (1.98-4.43)
			2 FDRs - 2 brothers	NR		15	2113	HR[c] = 6.29 (3.79-10.46)
			3 FDRs - Father + 2 brothers	NR		5	2113	HR[c] = 9.74 (4.05-23.43)
			3 FDRs – 3 brothers	NR		2	2113	HR[c] = 8.12 (2.03-32.50)
Utah cohort								
Beebe-Dimmer 2020	0-50 years	619,630	≥ 2 FDRs or SDRs on the same side of the family	77,078	< 2 FDRs or SDRs on the same side of the family diagnosed with prostate cancer N = 542,552	NR	NR	RR[b] = 1.70 (1.57-1.83)
Beebe-Dimmer 2020	0-50 years	619,630	≥ 3 relatives spanning 3 generations	11,104	< 2 FDRs or SDRs diagnosed with prostate cancer at age ≤ 55 years, or < 3 FDRs diagnosed with prostate cancer, or ≥ 3 relatives spanning 3 generations with prostate cancer N = 606,131	NR	NR	RR[b] = 1.97 (1.69-2.28)
Beebe-Dimmer 2020	0-50 years	619,630	≥ 2 FDRs or SDRs diagnosed with prostate cancer at age ≤ 55 years	893		NR	NR	RR[b] = 2.65 (1.84-3.81)
Beebe-Dimmer 2020	0-50 years	619,630	≥ 3 FDRs	2618		NR	NR	RR[b] = 3.02 (2.55-3.57)

CI = confidence interval; FDR = first degree relative; HR = hazard ratio; N = number; NR = not reported; RR = risk ratio; SDR = second degree relative; SMR = standardised mortality ratio; TDR = third degree relative

** Period (years) study population at risk of prostate cancer mortality assuming risk begins at age 40*

[a] Risk ratio based on observed versus expected rates in birth year and birth state cohort

[b] Risk ratio calculated using modified Poisson regression model which included birth year, birth state cohort and number of male relatives as covariables

[c] Hazard ratio calculated using Cox regression which included socioeconomic status, calendar period and region as covariates with age as underlying time scale – HR higher for younger cohorts

[d] Standardised mortality ratios standardised for age, calendar period, socioeconomic status and region

2.5 Risk of bias

The results of the risk of bias assessments for the included cohort studies are shown in Table 5.

Table 5. *Risk of bias assessments for included cohort studies using the ROBINS-E tool*

Study	*Risk of bias (ROBINS-E)*							
	Confounding	*Exposure measurement*	*Participant selection*	*Post-exposure interventions*	*Missing data*	*Outcome measurement*	*Reported result selection*	*Overall*
Albright 2017	Some concerns	Low	Some concerns	High	Low	Low	Low	High risk of bias
Brandt 2010	Low	Low	Low	High	Low	Low	Low	High risk of bias

Overall Rating

Low risk of bias except for concerns about uncontrolled confounding - *Low risk of bias except for concerns about uncontrolled confounding* in Domain 1 (Confounding) and *Low risk of bias* in all other domains

Some concerns - At least one domain is at *Some concerns*, but no domains are at *High risk of bias* or *Very high risk of bias*

High risk of bias - At least one domain is at *High risk of bias*, but no domains are at *Very high risk of bias* OR Several domains are at *Some concerns*, leading to an additive judgement of *High risk of bias*

Very high risk of bias - At least one domain is at *Very high risk of bias* OR Several domains are at *High risk of bias*, leading to an additive judgement of *Very high risk of bias*

3. GRADE assessment of the certainty of the evidence

Prostate cancer mortality – assessments are shown in Table 6

Table 6. *GRADE assessment of the certainty of the evidence as to whether the relative risk of prostate cancer mortality is greater than 2.0 for different prostate cancer family histories*

GRADE domain	Rating	Reason for rating	Certainty of evidence
*Exposure = relative **diagnosed** with prostate cancer*			
Risk of bias	No serious concerns	The single cohort study (Brandt 2010) reporting the risk of prostate cancer mortality for family histories of prostate cancer followed men from 1961-2006. PSA testing would have been available for at least 10 years of the 45 year study period. As a result there is a high risk of bias due to the likelihood that in the last 10 years of follow-up men with a family history of prostate cancer would have been more likely to have undergone PSA testing resulting in the earlier detection of prostate cancer and reducing the risk of prostate cancer mortality leading to underestimation of effect estimates. When determining whether the relative risk is greater than 2.0 this source of bias was considered not to impact the certainty of the evidence if the effect estimate is greater than 2.0 which is the case in this study when **one brother** has been diagnosed with prostate cancer, when **two brothers** have been diagnosed with prostate cancer, when **father diagnosed before age 65,** and when **father and one brother** have been diagnosed with prostate cancer.	*HIGH* *One brother diagnosed* *Two brothers diagnosed* *Father + brother diagnosed* *MODERATE* *Father diagnosed before age 65* *LOW* *Father diagnosed at any age or aged 65 or older*
	Serious concerns	Increased PSA testing as a result of family history will underestimate effect estimates therefore this source of bias was considered to impact the certainty of the evidence that the relative risk associated with an exposure is less than 2.0. This is the case in this study when of first degree relatives only **father** was diagnosed with prostate cancer at any age or diagnosed when aged 65 or older.	
Indirectness	No serious concerns	Results directly relevant	
Imprecision	No serious concerns	The confidence intervals for the risk ratios for **one brother** or **two brothers** diagnosed with prostate cancer did not cross 2.0. The lower limit of the confidence interval for **father + brother** diagnosed with prostate cancer was 1.98; in this instance there were concerns but not serious concerns that the effect estimate could be less than 2.0.	
	Serious concerns	The upper limit of the confidence interval for the risk ratio for **father** diagnosed with prostate cancer and for father diagnosed at age 65 or older crossed 2.0. The lower limit of the confidence interval for father diagnosed with prostate cancer before age 65 crossed 2.0.	
Inconsistency	Not Assessable	Not assessable as all results derived from a single cohort.	
Publication bias	Undetected	Could not be assessed as less than 10 studies. Publication bias considered unlikely as study reports risks for multiple different exposures	
*Exposure = relative **died of** prostate cancer*			
Risk of bias	No serious concerns	Two cohort studies reporting the risk of prostate cancer mortality for family histories of fatal prostate cancer followed men from 1961-2006 (Brandt 2010) and from 1966 to 2016 (Albright 2017), periods in which PSA testing would have been available for at least 10 of the 45 years and 20 of the 50 years of the study period, respectively. As a result they were considered at high risk of bias due to the likelihood that in the last 10 or 20 years of the study periods men with a family history of fatal prostate cancer would	*HIGH* *Most of the reported family histories of fatal prostate cancer*

		have been more likely to have undergone PSA testing resulting in the earlier detection of prostate cancer and reducing the risk of prostate cancer mortality leading to underestimation of effect estimates. When determining whether the relative risk is greater than 2.0 this source of bias was considered not to impact the certainty of the evidence if the effect estimate is greater than 2.0 which is the case in this study for the following family histories of fatal prostate cancer; • No first degree relatives and three or more second degree relatives • No first degree relatives and two or more second degree relatives • One first degree relative • One brother (based on CI of study with 398 events) • One first degree relative and one or more second degree relatives • Two first degree relatives • Two brothers • Father and one brother.	*MODERATE* *No first degree or second degree relatives but three or more third degree relatives died of prostate cancer* *No first degree relatives but one or more second degree relatives died of prostate cancer* *LOW* *Father died of prostate cancer*
	Serious concerns	Increased PSA testing as a result of family history will underestimate effect estimates therefore this source of bias was considered to impact the certainty of the evidence that the relative risk associated with an exposure is less than 2.0. This is the case in these studies for the following family histories of fatal prostate cancer; • No first degree or second degree relatives and three or more third degree relatives • No first degree relatives and one or more second degree relatives • Father.	
Indirectness	No serious concerns	Results directly relevant	
Imprecision	No serious concerns	The confidence intervals for the risk ratios for the following constellations of relatives who died of prostate cancer did not cross 2.0; • No first degree or second degree relatives and three or more third degree relatives • No first degree relatives and one or more second degree relatives • No first degree relatives and three or more second degree relatives • One first degree relative • One brother (based on CI of study with 398 events) • One first degree relative and one or more second degree relatives • Two first degree relatives • Two brothers • Father and one brother. The lower limit of the confidence interval for no first degree relatives and two or more second degree relatives was 1.98 – in this instance there were concerns but not serious concerns that the effect estimate could be less than 2.0.	
	Serious concerns	The confidence intervals for the risk ratios for the following constellations of relatives who died of prostate cancer crossed 2.0; • Father.	
Inconsistency	Not Assessable	Not assessable for exposures other than one brother died of prostate cancer and father died of prostate cancer as results for these exposures derived from a single cohort.	

	No serious concerns	Two studies reported effect estimates for men with one brother who had died of prostate cancer. Both studies reported effect estimates greater than 2.0 for this exposure. Two studies reported effect estimates for men whose father had died of prostate cancer. One study (Albright 2017) reported an effect estimate of 1.94 and the other (Brandt 2010) reported an effect estimate of 2.08. These differences may not be explained by different comparators (no family history of prostate cancer mortality versus no first degree relatives diagnosed with prostate cancer) but might be explained by shorter maximum follow-up in the study reporting the effect estimate of 2.08 if younger age of death of father is associated with a higher risk as is seen for younger age of diagnosis and differing impact of PSA testing due to differing durations of PSA testing availability and possibly uptake. Both effect estimates are within 10 percentage points of an effect estimate of 2.0 and likely reflect that the risk associated with this exposure is very close to 2.0.	
Publication bias	Undetected	Could not be assessed as less than 10 studies. Publication bias considered unlikely as both studies report risks for multiple different exposures.	

CI = confidence interval; PSA = prostate-specific antigen

4. Summary of findings

Table 7. *Summary of findings for the relative risk of prostate cancer mortality associated with different family histories of prostate cancer*

Outcome	***Time frame*****	***Cohorts (N)***	***Participants (N)***	***Comparator***	***Family History***	***No. prostate cancer deaths in exposed group***	***Study results and measurements (95%CI)***	***Certainty of evidence (GRADE)***	***Plain text summary***
*Exposure = relative/s **diagnosed** with prostate cancer*									
Prostate cancer mortality	Variable 0 - 34 years	1	3.9 million	No FDRs diagnosed with prostate cancer	1 FDR - father	306	HR = 1.81 (1.61-2.04)	Low[1]	The risk of prostate cancer mortality associated with having a father but not a brother diagnosed with prostate cancer may be less than double the risk than if no first-degree relatives diagnosed with prostate cancer overall, but is probably double or greater the risk than if no first-degree relatives diagnosed with prostate cancer if the father was diagnosed before 65 years of age.
					1 FDR - father diagnosed aged < 60 years	7	HR = 2.06 (0.98-4.32)	Moderate[3]	
					1 FDR - father diagnosed aged 60-64 years	23	HR = 2.55 (1.69-3.85)		
					1 FDR father diagnosed with prostate cancer aged 65-74 years	105	HR = 1.97 (1.62-2.40)	Low[1]	
					1 FDR - father diagnosed with prostate cancer aged 75-82 years	112	HR = 1.67 (1.38-2.10)		
					1 FDR - father diagnosed aged > 82 years	59	HR = 1.63 (1.26-2.12)		
					1 FDR - 1 brother	139	HR = 2.75 (2.32-3.26)	High	The risk of prostate cancer mortality associated with having only one brother but not a father diagnosed with prostate cancer is greater than double the risk if no first-degree relatives
					1 FDR - 1 brother diagnosed aged < 60 years	32	HR = 3.27 (2.31-4.64)		
					1 FDR - 1 brother diagnosed aged 60-64 years	44	HR = 2.55 (1.89-3.44)	Moderate[3]	

					1 FDR - 1 brother diagnosed aged 65-74 years	63	HR = 2.67 (2.08-3.43)	High	diagnosed with prostate cancer overall and if the brother was diagnosed before 60 years or at 65-74 years of age. It is probably greater than double the risk if no first-degree relatives diagnosed with prostate cancer if the brother was diagnosed between 60-64 years of age.
					2 FDRs - father + 1 brother	24	HR = 2.96 (1.98-4.43)	High	The risk of prostate cancer mortality associated with having a father and a brother diagnosed with prostate cancer is greater than double the risk if no first-degree relatives diagnosed with prostate cancer.
					2 FDRs - 2 brothers	15	HR = 6.29 (3.79-10.46)	High	The risk of prostate cancer mortality associated with having two brothers diagnosed with prostate cancer is greater than double the risk if no first-degree relatives diagnosed with prostate cancer.
*Exposure = relative/s **died from** prostate cancer*									
Prostate cancer mortality	Variable 0 - > 40 years	1	686,203	No family history of prostate cancer mortality	0 FDR or SDR ≥ 3 TDR	94	RR = 1.63 (1.32-2.00)	Moderate[2]	The risks of prostate cancer mortality associated with having three or more third-degree relatives but no first- or second-degree relatives who have died of prostate cancer, or one or more second-degree relatives but no first-degree relatives who have died of prostate cancer are probably less than double the risk if no family history of prostate cancer mortality.
					0 FDR ≥ 1 SDR	435	RR = 1.65 (1.50-1.81)		
					0 FDR ≥ 2 SDRs	71	RR = 2.54 (1.98-3.20)	High	The risk of prostate cancer mortality associated with having two or more second degree relatives but no first-degree relatives who have died of prostate cancer is greater than double the risk if no family history of prostate cancer mortality.
					0 FDR ≥ 3 SDRs	11	RR = 4.49 (2.24-8.03)	High	The risk of prostate cancer mortality associated with having three or more second-degree relatives but no first-degree
					1 FDR	475	RR = 2.49 (2.27-2.73)		
					1 FDR ≥ 1 SDR	83	RR = 3.18 (2.53-3.94)		
					2 FDRs	63	RR = 5.15 (3.96-6.59)		

	Variable 0 - > 40 years	1	686,203	No family history of prostate cancer mortality	2 FDRs - 2 brothers died of prostate cancer	45	RR = 4.63 (3.38-6.20)		relatives, or one or more first-degree relatives, or one first-degree relative and one or more second-degree relatives who have died of prostate cancer is greater than double the risk if either no family history of prostate cancer mortality or no first-degree relatives diagnosed with prostate cancer.
	Variable 0 - 34 years	1	3.9 million	No FDRs diagnosed with prostate cancer	2 FDRs - father + 1 brother died of prostate cancer	4	HR = 6.86 (2.57-18.28)		
	Variable 0 - > 40 years	1	686,203	No family history of prostate cancer mortality	Father died of prostate cancer	61	RR = 1.94 (1.49-2.50)*	Low[1]	The risk of prostate cancer mortality associated with having a father but no brothers who has died of prostate cancer may be close to double the risk if either no family history of prostate cancer mortality or no first-degree relatives diagnosed with prostate cancer.
	Variable 0 - 34 years	1	3.9 million	No FDRs diagnosed with prostate cancer	Father died of prostate cancer	202	HR = 2.08 (1.80-2.41)*		
	Variable 0 - > 40 years	1	686,203	No family history of prostate cancer mortality	1 FDR - 1 brother died of prostate cancer	398	RR = 2.62 (2.37-2.89)*	High	The risk of prostate cancer mortality associated with having one brother but not father who has died of prostate cancer is greater than double the risk if either no family history of prostate cancer mortality or no first-degree relatives diagnosed with prostate cancer.
	Variable 0 - 34 years	1	3.9 million	No FDRs diagnosed with prostate cancer	1 FDR - 1 brother died of prostate cancer	15	HR = 2.30 (1.38-3.81)*		

CI = confidence interval; FDR = first degree relative; HR = hazard ratio; No. = number; NR = not reported; RR = risk or rate ratio; SDR = second degree relative; TDR = third degree relative

* Two effect estimates reported for a very similar exposure – meta-analyses not undertaken as would require more than one approximation as one study reports a risk ratio and the other a hazard ratio and the numbers of exposed and unexposed were not reported for one study

** Period (years) study population at risk of prostate cancer mortality assuming risk begins at age 40

[1] Downgraded by two levels due to serious concerns re: risk of bias due to those with family history more likely to undergo PSA testing during more recent period of follow-up which would reduce the reported effect estimate, and imprecision as confidence intervals crossed 2.0.

[2] Downgraded by one level due to serious concerns re: risk of bias due to those with family history more likely to undergo PSA testing during more recent periods of follow-up

[3] Downgraded by one level due to serious concerns re: imprecision

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APPENDICES

Appendix A: Literature search strategies

A.1 Search strategies used for the 2016 guidelines

Database: Medline database - Search terms used to identify systematic reviews and meta-analysis

#	*Searches*
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	exp pedigree/
5	exp heredity/
6	exp family health/
7	disease susceptibility/
8	medical history taking/
9	(brother$ or father$ or sibling$ or relative$ or hereditary).tw.
10	(famil$ adj3 (history or cluster$ or aggreg$ or associate$ or member$ or risk$ or factor$)).tw.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	3 and 11
13	limit 12 to (english language and humans and yr="1990-current")
14	meta-analysis/
15	review literature/
16	meta-analy$.tw.
17	metaanal$.tw.
18	(systematic$ adj4 (review$ or overview$)).mp.
19	meta-analysis.pt.
20	review.pt.
21	review.ti.
22	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	case report/
24	letter.pt.
25	historical article.pt.
26	23 or 24 or 25
27	22 not 26
28	13 and 27

The systematic review filter used was based on the Centre for Reviews and Dissemination strategy 2.2 published in Lee et al, (2012) An optimal search filter for retrieving systematic reviews and meta-analyses BMC Medical Research Methodology 12:51.

Database: Medline database - Search terms used to identify papers published after 2010

#	*Searches*
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/

3	1 or 2
4	exp pedigree/
5	exp heredity/
6	exp family health/
7	exp disease susceptibility/
8	exp medical history taking/
9	(famil$ adj3 (history or cluster$ or aggreg$ or associat$ or member$ or risk$ or factor$)).tw.
10	(hereditary adj3 (history or cluster$ or aggreg$ or associat$ or risk$ or factor$)).tw.
11	((brother$ or father$ or sibling$ or relative$ or uncle$) adj5 (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$))).tw.
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	3 and 12
14	limit 13 to (english language and humans and yr="2010-current")

Database: Medline database – Aboriginal and Torres Strait Islander search terms used

#	***Searches***
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

Database: Embase database - Search terms used to identify systematic reviews and meta-analysis

#	***Searches***
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp OR 'prostate cancer'
3	1 or 2
4	'family history'/exp
5	'cancer susceptibility'/exp
6	'heredity'/de
7	brother* OR father* OR sibling* OR relative* OR hereditary
8	famil* NEAR/3 (history OR cluster* OR aggreg* OR associat* OR member* OR risk* OR factor*)
9	4 OR 5 OR 6 OR 7 OR 8
10	[embase]/lim AND [1990-2014]/py AND [english]/lim AND [humans]/lim
11	3 AND 9 AND 10
12	'systematic review'/exp OR 'systematic review'
13	'meta analysis'/exp OR 'meta analysis'
14	meta NEXT/1 analys*
15	search*
16	review* NEAR/2 systematic*
17	12 OR 13 OR 14 OR 15 OR 16
18	11 AND 17

Database: Embase database - Search terms used to identify papers published after 2010

#	*Searches*
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp OR 'prostate cancer'
3	1 or 2
4	'family history'/exp
5	'cancer susceptibility'/exp
6	famil* NEAR/3 (history OR cluster* OR aggreg* OR associat* OR member* OR risk* OR factor*)
7	hereditary NEAR/3 (history OR cluster* OR aggreg* OR associat* OR risk* OR factor*)
8	(brother* OR father* OR sibling* OR relative* OR uncle*) NEAR/5 prostat*
9	4 or 5 or 6 or 7 or 8
10	[embase]/lim AND [2010-2014]/py AND [english]/lim AND [humans]/lim
11	3 and 9 and 10
12	'genetic polymorphism'/exp
13	11 not 12

Database: Embase database – Aboriginal and Torres Strait Islander search terms used

#	*Searches*
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

For Cochrane Database of Systematic Reviews – The Cochrane Library

Title, abstracts, keywords: "prostate"

Database: Database of Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP)

#	*Searches*
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

A.2 Search strategies used for the 2025 guidelines update

Databases: Medline and Embase databases (via Ovid platform) – search for systematic reviews

#	*Searches*
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).tw.
2	exp Prostatic Neoplasms/
3	1 or 2
4	*heredity/
5	*pedigree/
6	*medical history taking/
7	(brother$ or father$ or sibling$ or relative$ or hereditary or pedigree or family tree$ or familial or paternal).tw.
8	(hereditary adj3 (history or cluster$ or aggreg$ or associat$ or risk$ or factor$)).tw.
9	(famil$ adj3 (history or cluster$ or aggreg$ or associate$ or member$ or risk$ or factor$)).tw.
10	(risks or risk factors or risk assessment* or risk prediction*).ti.

11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	3 and 11
13	limit 12 to english language
14	limit 13 to human
15	limit 14 to yr="2014 -Current"
16	(docetaxel or chemotherapy or radiotherapy or castrat* or metabolic risk factor*).tw.
17	15 not 16
18	limit 17 to (conference abstract or conference paper or "conference review") [Limit not valid in Ovid MEDLINE(R); records were retained]
19	limit 18 to medline
20	18 not 19
21	17 not 20
22	(Systematic* adj3 review*).tw.
23	(meta-analys* or meta analys*).tw.
24	22 or 23
25	21 and 24
26	remove duplicates from 25

Databases: Medline and Embase databases (via Ovid platform) – search for original articles

#	*Searches*
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).tw.
2	exp Prostatic Neoplasms/
3	1 or 2
4	*heredity/
5	*pedigree/
6	*medical history taking/
7	(brother$ or father$ or sibling$ or relative$ or hereditary or pedigree or family tree$ or familial or paternal).tw.
8	(hereditary adj3 (history or cluster$ or aggreg$ or associat$ or risk$ or factor$)).tw.
9	(famil$ adj3 (history or cluster$ or aggreg$ or associate$ or member$ or risk$ or factor$)).tw.
10	(risks or risk factors or risk assessment* or risk prediction*).ti.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	3 and 11
13	limit 12 to english language
14	limit 13 to human
15	limit 14 to yr="2014 -Current"
16	(docetaxel or chemotherapy or radiotherapy or castrat* or metabolic risk factor*).tw.
17	15 not 16
18	limit 17 to (conference abstract or conference paper or "conference review") [Limit not valid in Ovid MEDLINE(R); records were retained]
19	limit 18 to medline
20	18 not 19
21	17 not 20

Appendix B: GRADE assessment of the certainty of the evidence

Ratings	*Definitions*
⨁⨁⨁⨁ High certainty	The panel is very confident that the true effect lies close to that of the estimate of the effect
⨁⨁⨁◯ Moderate certainty	The panel is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁◯◯ Low certainty	The panel's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁◯◯◯ Very low certainty	The panel has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reportedly based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Systematic reviews of the evidence were not accessible.
British Columbia	https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines	Prostate Cancer Part 1: Diagnosis and Referral in Primary Care	2020	Systematic reviews of the evidence were not accessible.
Canadian Urology Association	https://www.cua.org/guidelines	Canadian Urological Association (CUA): 2022 Recommendations on prostate cancer screening and early diagnosis	2022	Systematic reviews of the evidence were not accessible.

Appendix D: Excluded articles - 2016 guidelines searches

Article	*Reason for exclusion*
Albright 2012	No relevant comparisons
Bishop 1997	Narrative review comment – excluded publication type
Brandt 2010	Excluded study design
Bratt 1997	No relevant outcomes
Bratt 2000	Narrative review/comment – excluded publication type
Bratt 2002	Narrative review/comment – excluded publication type
Bratt 2007	Narrative review/comment – excluded publication type
Bratt 2010	No relevant outcomes
Bratt 2016	No relevant outcomes
Bruner 2003	Systematic review with different inclusion criteria
Cannon-Albright 1994	No relevant comparisons
Cerban 1999	Self-reported family history - no relevant exposure
Chen 2008	Self-reported family history - no relevant exposure
Colloca 2011	Narrative review/comment – excluded publication type
Cunningham 2003	Self-reported family history - no relevant exposure
Cussenot 1998	Narrative review/comment – excluded publication type
Damber 1999	Narrative review/comment – excluded publication type
Dong 2001	More mature data published – superseded
Eldon 2003	No relevant outcomes
Elshafei 2013	Self-reported family history - no relevant exposure
Frank 2014	No relevant outcomes
Gil-Bazo 2014	Excluded study design
Goldgar 1994	More mature data published – superseded
Gronberg 1996	No relevant outcomes
Gronberg 1999	No relevant outcomes
Hemminki 2000	More mature data published – superseded
Hemminki 2002a	More mature data published – superseded
Hemminki 2002b	More mature data published – superseded
Hemminki 2008	No relevant outcomes
Hemminki 2012	Narrative review/comment – excluded publication type
Hodgson 2013	Narrative review/comment – excluded publication type
Jansson 2012	Relevant data published previously – duplicate data

Johns 2003	Systematic review – superseded
Kalish 2000	Did not specify degree of family history - no relevant exposure
Kerber 2005	No relevant outcomes
Kicinski 2011	Systematic review with different inclusion criteria
Kharazmi 2012	No relevant outcomes
Kral 2011	Narrative review/comment – excluded publication type
Liang 2013	No relevant comparisons
Madersbacher 2011	Narrative review/comment – excluded publication type
Mai 2010	No relevant comparisons
Makinen 2002	Self-reported family history - no relevant exposure
Matikainen 2001	No relevant outcomes
McLellan 1995	Systematic review with different inclusion criteria
Monroe 1995	No relevant comparisons
Muller 2013	Did not specify degree of family history – no relevant exposure
Narod 1995	Self-reported family history – no relevant exposure
Noe 2008	Narrative review/comment – excluded publication type
Park 2009	Did not specify degree of family history – no relevant exposure
Pienta 1993	Narrative review/comment - excluded publication type
Randazzo 2014	Conference abstract - excluded publication type
Rodriguez 1997	Self-reported family history – no relevant exposure
Romero 2013	Self-reported family history – no relevant exposure
Roobol 2009	Narrative review/comment – excluded publication type
Stanford 2001	Narrative review/comment – excluded publication type
Turati 2013	Excluded study design
Zeegers 2003	Systematic review with different inclusion criteria
Zoller 2014	No relevant outcomes
Xu 2021	No relevant outcomes
Xu 2022	Excluded study design

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Appendix E: Excluded articles - 2025 searches

Article	*PMID/DOI*	*Reason for exclusion*
Abdel-Rahman 2019	https://doi.org/10.1016/j.clgc.2019.05.015	No relevant exposure
Albertsen 2016	https://doi.org/10.1200/JCO.2016.70.4742	Excluded publication type
Albright 2015	https://doi.org/10.1002/pros.22925	No relevant outcomes
Amini 2024	https://doi.org/10.1200/po.23.00560	Excluded study design
Ankerst 2014	https://doi.org/10.1016/j.urology.2014.02.035	No relevant exposure
Barber 2018	https://doi.org/10.1158/1078-0432.ccr-18-0370	No relevant exposure
Ber 2022	https://doi.org/10.1097/ju.0000000000002761	Excluded publication type
Berenguer 2023	https://pubmed.ncbi.nlm.nih.gov/36826139/	Excluded study design
Bergengren 2023	https://doi.org/10.1016/j.eururo.2023.04.021	Not a systematic review
Bratt 2016	https://doi.org/10.1093/jnci/djw110	No relevant outcomes
Brook 2023	https://doi.org/10.1016/j.eururo.2022.11.019	Wrong patient population
Brook 2023	https://doi.org/10.1016/j.eururo.2023.04.001	Excluded publication type
Carter 2015	https://doi.org/10.1016/j.juro.2014.09.114	Excluded publication type
Chen 2016	https://doi.org/10.1002/pros.23200	No relevant exposure
Cheng 2024	https://doi.org/10.1186/s12967-024-05190-y	No relevant exposure
Choi 2021	https://pubmed.ncbi.nlm.nih.gov/33607822/	No relevant outcomes
Clements 2022	https://doi.org/10.1016/j.eururo.2021.12.011	Wrong patient population
Conran 2016	https://doi.org/10.4103/1008-682x.179527	Wrong patient population
Cui 2024	https://doi.org/10.1371/journal.pmed.1004362	No relevant exposure
Dite 2023	https://doi.org/10.1002/pros.24537	No relevant outcomes
Fiederling 2016	https://doi.org/10.1002/ijc.30203	No relevant exposure
Giri 2016	https://doi.org/10.1053/j.seminoncol.2016.08.001	Excluded study design
Graham 2025	https://doi.org/10.1016/j.urolonc.2024.06.002	Wrong patient population
Grill 2015	https://pubmed.ncbi.nlm.nih.gov/25242395/	No relevant outcomes
HaChung 2019	https://doi.org/10.1016/j.prnil.2018.11.001	Excluded study design
Hassanin 2022	https://doi.org/10.1016/j.gim.2021.11.009	No relevant outcomes
Hemminki 2021	https://doi.org/10.3390/cancers13174385	No relevant outcomes
Hemminki 2023	https://doi.org/10.1016/j.eururo.2023.03.039	Excluded publication type
Hemminki 2023	https://doi.org/10.1186/s13053-023-00247-3	Excluded study design
Hemminki 2024	https://doi.org/10.1016/j.euros.2024.08.011	Excluded publication type
Hidaka 2020	https://doi.org/10.1002/ijc.32724	No relevant outcomes
Hippisley-Cox 2015	https://doi.org/10.1136/bmjopen-2015-007825	No relevant outcomes
Hippisley-Cox 2021	https://doi.org/10.3399/bjgp20x714137	No relevant exposure
Huynh-Le 2021	https://doi.org/10.1038/s41391-021-00341-4	No relevant exposure
Hwang 2023	https://doi.org/10.1186/s12894-023-01259-w	No relevant outcomes
Kim 2018	https://doi.org/10.4143/crt.2017.484	No relevant outcomes
Klein 2022	https://doi.org/10.1038/s41698-022-00266-8	No relevant exposure
Lee 2015	https://doi.org/10.1002/ijc.29239	No relevant outcomes
Liss 2015	https://doi.org/10.1016/j.juro.2014.07.085	No relevant exposure
Lorentz 2024	https://doi.org/10.5489/cuaj.8710	Excluded study design
Markt 2022	https://doi.org/10.1016/j.eururo.2022.01.030	Excluded publication type
Meissner 2020	https://doi.org/10.1159/000504789	Wrong patient population

Michael 2022	https://doi.org/10.5534/wjmh.220068	Wrong patient population
Munoz 2016	https://pubmed.ncbi.nlm.nih.gov/27428752/	No relevant outcomes
NiRaghallaigh 2022	https://doi.org/10.1007/s10689-021-00227-3	Excluded study design
Nyberg 2023	https://doi.org/10.1200/jco.22.01453	No relevant outcomes
Pagniez 2020	https://doi.org/10.1097/ju.0000000000000757	No relevant exposure
Perez-Cornago 2017	https://doi.org/10.1038/bjc.2017.312	No relevant exposure
Plym 2022	https://doi.org/10.1158/1078-0432.ccr-22-1723	No relevant exposure
Plym 2024	https://doi.org/10.1001/jamanetworkopen.2024.20034	No relevant exposure
Randazzo 2016	https://doi.org/10.1111/bju.13310	No relevant exposure
Ren 2019	https://doi.org/10.1186/s12885-019-6055-9	No relevant exposure
Roobol 2017	https://doi.org/10.1016/j.eururo.2017.01.033	No relevant exposure
Saarimaki 2015	https://doi.org/10.1002/ijc.29243	Wrong patient population
Seibert 2018	https://doi.org/10.1136/bmj.j5757	No relevant exposure
Shi 2021	https://doi.org/10.1016/j.eururo.2020.11.014	No relevant exposure
Ventimiglia 2017	https://doi.org/10.1016/j.eururo.2016.08.063	Excluded publication type
Vertosick 2014	https://doi.org/10.1016/j.juro.2014.03.032	Excluded study design
Xu 2020	https://doi.org/10.1038/s41391-019-0165-y	Excluded study design
Xu 2021	https://doi.org/10.1016/j.eururo.2021.04.043	Excluded publication type
Xu 2021	https://doi.org/10.1371/journal.pmed.1003616	No relevant outcomes
Xu 2022	https://doi.org/10.1038/s41391-021-00458-6	Excluded study design
Yeo 2022	https://pubmed.ncbi.nlm.nih.gov/35055319/	No relevant exposure
Zhang 2023	https://pubmed.ncbi.nlm.nih.gov/37139178/	No relevant exposure
Zheng 2022	https://doi.org/10.1002/cam4.4591	No relevant outcomes

3.2 Clinical question 2 – Black males of sub-Saharan ancestry

Clinical question: *What is the risk of diagnosis of clinically significant prostate cancer or prostate cancer-specific mortality for those of sub-Saharan African ancestry compared with the risk for the those of other ancestries, overall and by age groups in Australia?*

Systematic review report on the relative risks of clinically significant prostate cancer or prostate cancer-specific mortality for individuals in Australia of Sub-Saharan African ancestry

Authors

Harriet Hui, Suzanne Hughes

PECO

This systematic review addresses the following PECO which is summarised in detail in Table 1.

For asymptomatic individuals in Australia, what is the risk of being diagnosed with clinically significant prostate cancer or prostate cancer-specific mortality, overall and by age group, for individuals of Sub-Saharan African ancestry when compared to individuals of other ancestries?

Table 4. *PECO components*

Population	***Exposure***	***Comparator***	***Outcomes***	***Study design***
Individuals in Australia at risk of prostate cancer without a prostate cancer diagnosis or symptoms that might indicate prostate cancer	Sub-Saharan African ancestry	Ancestry other than Sub-Saharan African or Australian population	Prostate cancer mortality or Clinically significant prostate cancer diagnosis • Overall • By age group	Cohort or Nested case-control or Systematic reviews thereof

1. Methods

1.1 Selection Criteria

Table 5. *Selection criteria for systematic review of the relative risks of clinically significant prostate cancer and prostate cancer mortality for individuals in Australia of Sub-Saharan African ancestry*

Selection criteria	***Inclusion criteria***	***Exclusion criteria***
Study type	Aetiology /risk factor	
Study design	Cohort studies (prospective or retrospective) (including AIHW data) Nested case-control studies Systematic reviews of above	Case-control studies Non-systematic reviews
Population	People in Australia at risk of prostate cancer without a history of prostate cancer or symptoms that might indicate prostate cancer	Population subgroups other than specific age groups e.g. restricted to smokers or those with a pre-existing health condition
Exposure	Sub-Saharan African ancestry	
Comparator/ Reference group	Ancestry other than Sub-Saharan ancestry General population	
Outcomes	Clinically significant prostate cancer diagnosis/incidence or Prostate cancer mortality • Overall • By age	Any prostate cancer Prostate cancer survival Metastatic disease
Analyses	Considers age in analyses	
Language	English	
Publication period	1990 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof more recent data AIHW data	Conference abstract Editorial Letter or article that does not report original data

AIHW = Australian Institute of Health and Welfare

1.2 Definitions and terminology

For the purposes of this review:

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).

1.3 Guidelines searches

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- BIGG international database of GRADE guidelines database
- Guidelines International Network (GIN) database
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Urological Society of Australia and New Zealand (USANZ) website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

The Australian Institute of Health and Welfare (AIHW) website was searched for relevant data using the search terms “Africa” and “African” on 13th December 2024. Medline and Embase databases were searched on 26th November 2024 combining terms for prostate cancer, Africa and Australia to identify relevant studies. A complete list of the terms used in the search is included as Appendix A. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

The following study characteristics were to be extracted; study design, population age and geographical location, study period, databases used, exposure ascertainment, comparator population, relevant outcomes reported and subgroup data available, and confounders considered in analyses. The following results were to be extracted; rates of outcomes for exposed and comparator populations, effect estimates and 95% confidence intervals as reported in the study or calculated using relevant reported data. Subgroup analyses were planned for age groups if available.

1.6 Risk of bias assessments

Independent assessments of the risk of bias by two reviewers using the ROBINS-E tool (ROBINS-E Development Group 2023) were planned.

1.7 GRADE assessment of the certainty of the evidence

GRADE assessments were planned to assess the certainty of the body of evidence for each outcome. (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence would be rated high, moderate, low or very low based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance for assessing narrative syntheses provided by Murad 2017 and prognostic studies provided by Foroutan 2020 with additional guidance for the assessment of imprecision provided by Schunemann 2022. As per GRADE guidance for prognostic studies (Foroutan 2020), studies started with a high level of certainty in the evidence and were to be downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

Definitions of the GRADE ratings of certainty are presented in Appendix B.

2. Results

2.1 Guidelines searches

No relevant guidelines based on systematic reviews of the literature were identified.

2.2 Literature searches

No relevant AIHW data was identified.

The search for potentially relevant articles identified 117 unique records (Figure 1). Of these, 11 were selected for full text review. None met the criteria for inclusion in our systematic review.

The retrieved articles that were not included in this systematic review and the reasons for their exclusion are documented in Appendix C. The main reason for exclusion was publication type.

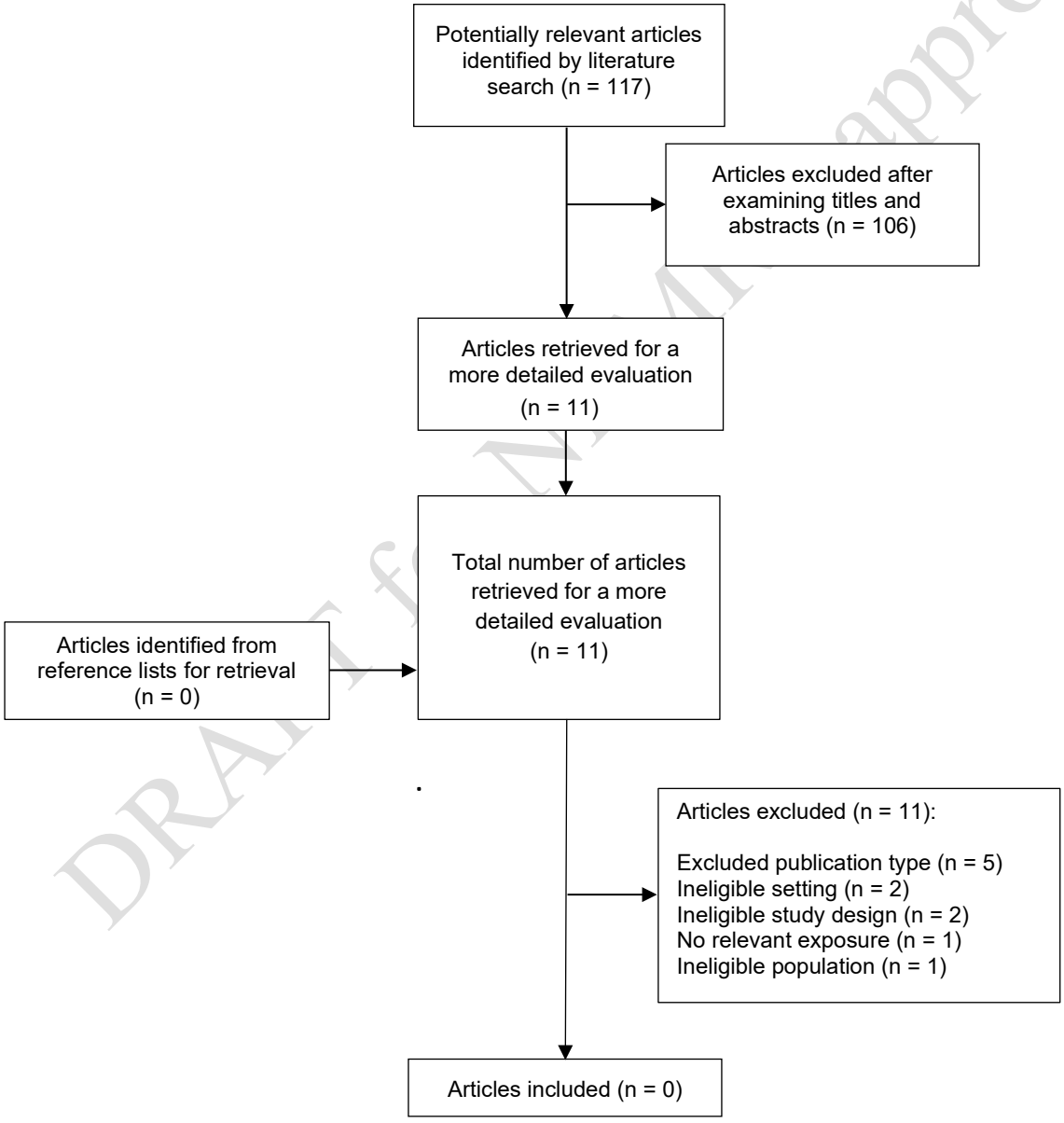

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

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APPENDICES

Appendix A: Literature search strategy

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	(prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or metast* or adeno*)).tw.
2	(Africa* or Ethiopia* or Somali*).tw.
3	Australia*.tw.
4	(New south wales or NSW).tw.
5	(Victoria* or vic).tw.
6	(Queensland or QLD).tw.
7	(Tasmania or Tas).tw.
8	northern Territory.tw.
9	Australia.in.
10	3 or 4 or 5 or 6 or 7 or 8 or 9
11	1 and 2 and 10
12	remove duplicates from 11

Appendix B: GRADE assessment of the certainty of the evidence

Ratings	*Definitions*
⊕⊕⊕⊕ High certainty	The panel is very confident that the true effect lies close to that of the estimate of the effect
⊕⊕⊕◯ Moderate certainty	The panel is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ Low certainty	The panel's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕◯◯◯ Very low certainty	The panel has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Appendix C: Excluded Studies

Article	*DOI/Link*	*Reason for exclusion*
Mahumud 2023	https://doi.org/10.1371/journal.pone.0228744	Excluded publication type
Arigbede 2024	https://doi.org/10.1158/1538-7755.DISP24-C001	Excluded publication type
Conti 2021	https://doi.org/10.1038/s41588-020-00748-0	Ineligible setting
Culp 2020	https://doi.org/10.1016/j.eururo.2019.08.005	No relevant exposure
Dantanarayana 2015	https://doi.org/10.1186/s12894-015-0117-3	Ineligible population
de-Graft Aikins 2023	https://doi.org/10.1371/journal.pone.0277325	Ineligible study design
Hayes 2023	https://doi.org/10.1017/thg.2023.7	Excluded publication type
Hayes 2023	https://doi.org/10.1002/ctm2.1142	Excluded publication type
Marima 2021	https://pmc.ncbi.nlm.nih.gov/articles/PMC8085879/	Ineligible study design
Petersen 2019	https://doi.org/10.1186/s12920-019-0537-0	Ineligible setting
Soh 2023	https://doi.org/10.1016/j.eururo.2023.04.006	Excluded publication type

3.3 Clinical question 3 – Aboriginal and Torres Strait Islander Peoples

Clinical question: *What is the risk of diagnosis of clinically significant prostate cancer or prostate cancer-specific mortality for those who identify as Aboriginal and Torres Strait Islander people compared with the risks for the those who do not, overall and by age groups?*

Systematic review report on the relative risks of clinically significant prostate cancer or prostate cancer-specific mortality for individuals who identify as Aboriginal or Torres Strait Islander peoples

Authors

Suzanne Hughes, Susan Yuill, Harriet Hui, Karen Chiam, Visalini Nair-Shalliker

PECO

This systematic review addresses the following PECO which is summarised in detail in Table 1.

For asymptomatic individuals in Australia, what is the risk of being diagnosed with clinically significant prostate cancer or prostate cancer-specific mortality overall and by age group for those who identify as Aboriginal or Torres Strait Islander peoples when compared to individuals who do not identify as Aboriginal or Torres Strait Islander peoples?

Table 6. *PECO components*

Population	***Exposure***	***Comparator***	***Outcomes***	***Study design***
Individuals in Australia at risk of prostate cancer without a prostate cancer diagnosis or symptoms that might indicate prostate cancer	Identify as Aboriginal or Torres Strait Islander peoples	Do not identify as Aboriginal or Torres Islander peoples or Australian population	Prostate cancer mortality or Clinically significant prostate cancer diagnosis • Overall • By age group	Cohort or Nested case-control or Systematic reviews thereof

1. Methods

1.1 Selection Criteria

Table 7. *Selection criteria for systematic review of the relative risks of clinically significant prostate cancer and prostate cancer mortality for individuals who identify as Aboriginal or Torres Strait Islander peoples*

Selection criteria	***Inclusion criteria***	***Exclusion criteria***
Study type	Aetiology /risk factor	
Study design	Cohort studies (prospective or retrospective) (including most recent AIHW data) Nested case-control studies Systematic reviews of above	Case-control studies Non-systematic reviews
Population	People in Australia at risk of prostate cancer without a history of prostate cancer or symptoms that might indicate prostate cancer	Population subgroups other than specific age groups eg restricted to smokers or those with a pre-existing health condition
Exposure	Identify as Aboriginal or Torres Strait Islander peoples	
Comparator/ Reference group	Do not identify as Aboriginal or Torres Islander peoples General population	
Outcomes	Clinically significant prostate cancer diagnosis/incidence or Prostate cancer mortality • Overall • By age	Any prostate cancer Prostate cancer survival Metastatic disease
Analyses	Considers age in analyses	
Language	English	
Publication period	1990 onwards	
Publication type	Most recent AIHW data Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof that augments most recent AIHW data eg reports • results where important confounders in addition to age were considered in the analyses • more recent data • results for regional subpopulations	Conference abstract Editorial Letter or article that does not report original data

AIHW = Australian Institute of Health and Welfare

1.2 Definitions and terminology

For the purposes of this review:

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).

1.3 Guidelines searches

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- BIGG international database of GRADE guidelines database
- Guidelines International Network (GIN) database
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website

- Urological Society of Australia and New Zealand (USANZ) website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

The Australian Institute of Health and Welfare (AIHW) website was searched for the most recent relevant age-standardised data. Medline and Embase databases were searched on 26th November 2024 combining terms for prostate cancer and Aboriginal and Torres Strait Islander peoples to identify results published after AIHW data, results for regional or remote communities and results where important confounders in addition to age were considered in the analyses. A complete list of the terms used in the search is included as Appendix A. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

One reviewer extracted the relevant data from the AIHW data tables and the included studies. A second reviewer checked the extracted data. The following characteristics of the included studies and AIHW data were extracted: population age and geographical location, study period, databases used, exposed population, comparator population, relevant outcomes reported and subgroup data available, and confounders considered in analyses. Rates of outcomes for exposed and comparator populations, and effect estimates and their 95% confidence intervals (95% CIs) were extracted or calculated. Subgroup analyses were planned for age groups if available. Where only age-standardised rates were published, age-standardised rate ratios and their 95% CIs were calculated using methods for incidence rate ratios at https://influentialpoints.com/Training/confidence_intervals_of_risk_ratio_odds_ratio_and_rate_ratio-principles-properties-assumptions.htm

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias of each included study with differences resolved by discussion using the ROBINS-E tool (ROBINS-E Development Group 2023). The overall risk of bias of studies was rated low except for concerns about uncontrolled confounding (as studies are observational, the possibility of uncontrolled confounding cannot be eliminated), some concerns, high or very high based on assessments of the risk of bias associated with the following sources of bias: confounding, measurement of exposure, participant selection, post-exposure interventions, missing data, measurement of the outcome, and

reported result selection. Prespecified important confounders were age, geography (remoteness), socioeconomic status/education, period, PSA testing behaviours and life expectancy.

1.7 GRADE assessment of the certainty of the evidence

A GRADE (grading of recommendation, assessment, development and evaluation) approach was used to assess the certainty of the body of evidence for the outcomes of prostate cancer mortality and clinically significant prostate cancer (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness of the results, imprecision, inconsistency of the results, and publication bias based on guidance for assessing narrative syntheses provided by Murad 2017 and prognostic studies provided by Foroutan 2020 with additional guidance for the assessment of imprecision provided by Schunemann 2022. Imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. These thresholds were determined by the MCID Working Group, a reference group consisting of a consumer, a general practitioner, a urology nurse practitioner and clinical specialists, following GRADE guidance provided by Schunemann 2022. Where there was only one study inconsistency could not be rated. Where there were less than 10 studies, publication bias was assessed based on a consideration of potential conflicts of interest.

As per GRADE guidance for prognostic studies (Foroutan 2020), studies started with a high level of certainty in the evidence and were downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias. Definitions of the GRADE ratings of certainty are presented in Appendix B.

2. Results

2.1 Guidelines searches

No relevant guidelines based on systematic reviews of the literature were identified.

2.2 Literature searches

Relevant AIHW data as of January 2023 was identified in the data files accompanying the section on cancer in Aboriginal and Torres Strait Islander Health Performance Framework Report 2024 https://www.indigenoushpf.gov.au/measures/1-08-cancer.

The search for published articles with additional data identified 172 unique records (Figure 1). Of these, 28 were identified as potentially relevant and the full text of these articles were assessed independently by two reviewers. One article met the criteria for inclusion in our systematic review (Coory 2000). No additional articles were identified from its reference list.

The retrieved articles that were not included in this systematic review and the reasons for their exclusion are documented in Appendix C. The main reason for exclusion was no population of interest.

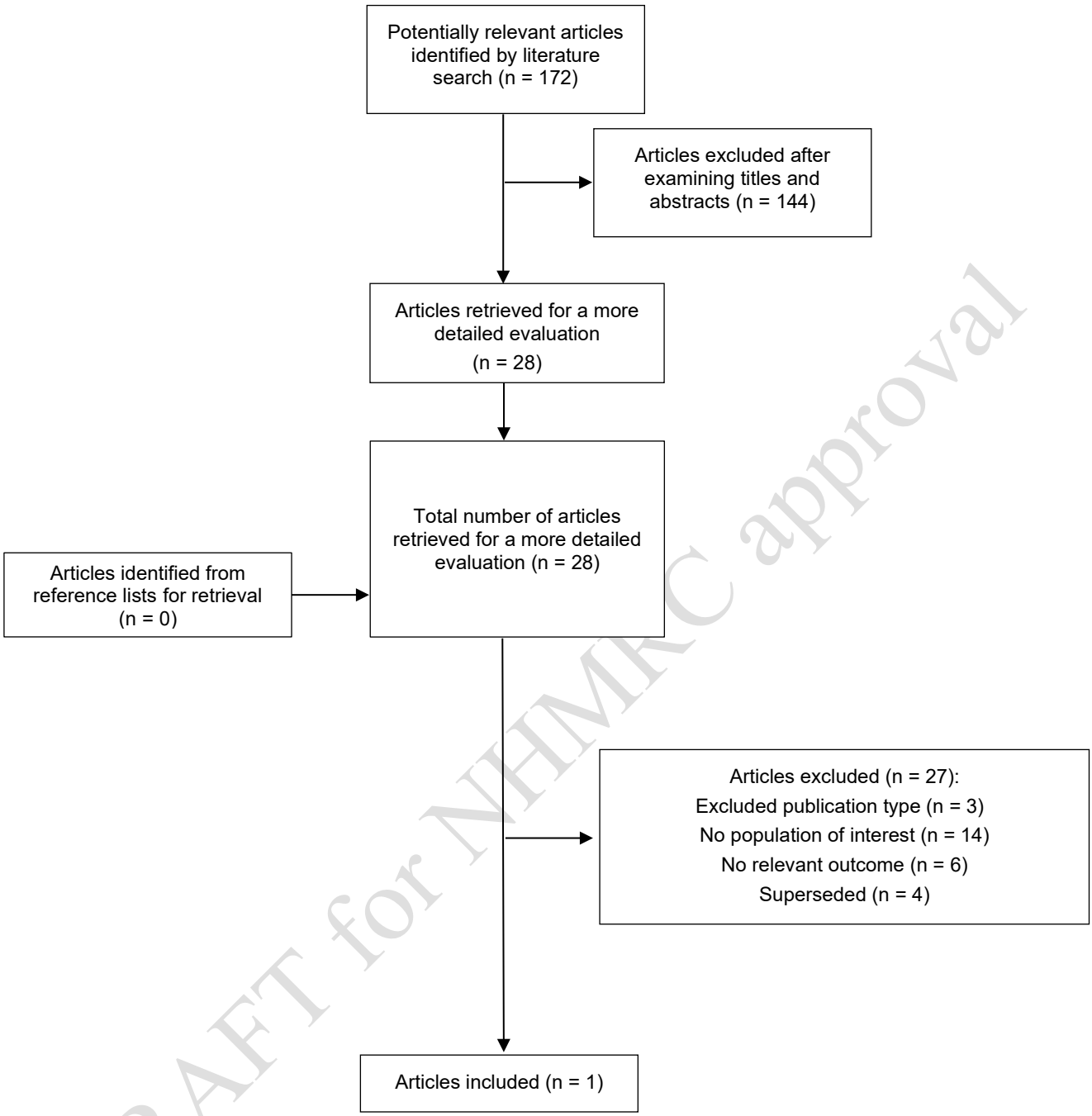

Figure 1. *Process of inclusion and exclusion of published articles for the systematic review*

2.3 Characteristics of included data and study

Table 8. *Characteristics of most recent AIHW data and additional included study reporting risks of clinically significant prostate cancer and prostate cancer mortality for individuals who identify as Aboriginal and Torres Strait Islander*

Study/ AIHW Data	***Population***	***Study/ AIHW data period***	***Exposed population***	***Comparator population***	***Relevant outcome***	***Important confounders considered in analyses***	***Comments***
AIHW 2024	New South Wales, South Australia, Western Australia, Queensland and Northern Territory populations estimated using 2016 census data The AIHW considered these jurisdictions to have adequate levels of Indigenous identification in mortality data. No restrictions on age	2015-2019	***Indigenous population*** The 2016 Census-based Aboriginal and Torres Strait Island population estimates. ***Indigenous deaths*** ascertained by Aboriginal or Torres Strait Islander status on the Death Registration Form and/or the Medical Certificate of Cause of Death*	***Non-Indigenous population*** Derived by subtracting the 2016 Census-based Aboriginal and Torres Strait Island population estimates from the total 2016 Census-based estimated resident population. ***Non-Indigenous deaths*** ascertained by Aboriginal or Torres Strait Islander status on the Death Registration Form and/or Medical Certificate of Cause of Death*	Prostate cancer mortality based on underlying cause recorded by State Registrars of Births Deaths and Marriages death registration form and/or the National Coronial Information System	Age *Directly age-standardised using the 2001 Australian standard population, by 5-year age groups up to 75+*	AIHW acknowledged that not all Aboriginal and Torres Strait Islander deaths "*are captured through their processes, leading to under-identification"*.* And that *"Data presented in this publication may therefore underestimate the level of Aboriginal and Torres Strait Islander deaths and mortality in Australia"*.* Excluded *"Deaths for which the age at death was not recorded were excluded from the calculation of age-standardised rates.* *3,577 registered deaths where the Indigenous status was not stated over the period 2015–2019"* (0.6% of registered deaths)
Coory 2000	Queensland population based on 1996 Census data? No restrictions on age	1982-1996	***Rural and remote Indigenous populations*** People living in 13 rural or remote communities (excluding the Torres Strait Islands) 92% self-identified as Indigenous in 1996 Census ***Indigenous cancer deaths*** ascertained by address at diagnosis and linked cancer death in	***Queensland population*** People living in Queensland in 1996 Census **Queensland cancer deaths** ascertained from Queensland Cancer Registry	Prostate cancer mortality ascertained from Queensland Cancer Registry 1982-1996	Age Period Indirectly age-standardised for 5-year periods to total Queensland population PSA testing as undertaken in pre-PSA testing era Unclear as to source of population age groups – Census data?	

			Queensland Cancer Registry				

Data used by AIHW to calculate ASMR https://www.abs.gov.au/methodologies/causes-death-australia-methodology/2019#deaths-of-aboriginal-and-torres-strait-islander-people
AIHW = Australian Institute of Health and Welfare

2.4 Results by outcomes of interest

Prostate cancer mortality – results presented in Table 4

Clinically significant prostate cancer – no relevant results found

Table 4. *Results of AIHW data and cohort study reporting risks of prostate cancer mortality associated with Aboriginal and Torres Strait Islander status*

	Outcome	***Exposed population***	***Comparator population***	***Effect estimate (95%CI)***
NSW, QLD, NT, WA and SA - Indigenous vs Non-Indigenous				
AIHW 2024	Prostate cancer mortality 2015-2018	ASMR = 24.6/100,000	ASMR = 25.3/100,000	SMRR = 0.97 (0.56-1.69)
QLD - Remote and rural Indigenous communities vs QLD population				
Coory 2000	Prostate cancer mortality 1982-1996	6/12,627 (observed)	5.6/12,627 (expected)	SMR = 1.06 (0.39-2.32)

ASMR = age-standardized mortality rate; CI = confidence interval; SMRR = standardized mortality rate ratio; SMR = standardized mortality ratio

2.5 Risk of bias

The results of the risk of bias assessments for the included AIHW data and study are shown in Table 5.

Table 5. *Risk of bias assessments for included data and study using the ROBINS-E tool*

Study	*Risk of bias (ROBINS-E)*							
	Confounding	*Exposure measurement*	*Participant selection*	*Post-exposure interventions*	*Missing data*	*Outcome measurement*	*Reported result selection*	*Overall*
AIHW data 2023	High	Some concerns	Some concerns	Some concerns	High	Low	Low	High risk of bias
Coory 2000	High	High	Some concerns	Some concerns	High	Low	Some concerns	High risk of bias

Overall Rating

Low risk of bias except for concerns about uncontrolled confounding - *Low risk of bias except for concerns about uncontrolled confounding* in Domain 1 (Confounding) and *Low risk of bias* in all other domains

Some concerns - At least one domain is at *Some concerns*, but no domains are at *High risk of bias* or *Very high risk of bias*

High risk of bias - At least one domain is at *High risk of bias*, but no domains are at *Very high risk of bias* OR Several domains are at *Some concerns*, leading to an additive judgement of *High risk of bias*

Very high risk of bias - At least one domain is at *Very high risk of bias* OR Several domains are at *High risk of bias*, leading to an additive judgement of *Very high risk of bias*

3. GRADE assessment of the certainty of the evidence

Prostate cancer mortality – assessments are shown in Table 6

Table 6. *GRADE assessment of the certainty of the evidence for the relative risk of prostate cancer mortality for Indigenous peoples of Australia*

GRADE domain	*Rating*	*Reason for rating*	*Certainty of evidence*
NSW, QLD, NT, WA and SA - Indigenous vs Non-Indigenous			
Risk of bias	*Very serious concerns*	Age, socioeconomic status/education, screening behaviours, geography (rural/remote vs urban), period and differing life expectancies were considered important confounders. For a single set of data reporting this outcome (AIHW 2023), there were very serious concerns regarding confounding due to possible differences in socioeconomic status/education, PSA testing behaviours, geographical location, and life expectancy.	*LOW*
Indirectness	*No serious concerns*	Results directly relevant and relatively recent	
Imprecision	*No serious concerns*	Based on a standardised mortality rate ratio of 0.97 with 95% confidence interval of 0.56 to 1.69, in a population of 100,000 men, it is estimated that there will be 1 less (11 less, 18 more) prostate cancer deaths among men who identify as Aboriginal and Torres Strait Islander peoples when compared with those who do not identify as Aboriginal and Torres Strait Islander peoples. Using a MCID of 50 prostate cancer deaths over a 5-year period/100,000 and thresholds for moderate and large effects of 100 and 200 deaths/100,000, the absolute difference between the two groups was not clinically important, and its 95%CI did not cross any thresholds.	
Inconsistency	*Not Assessable*	Not assessable as only a single set of data.	
Publication bias	*Undetected*	Only one set of data and data published by AIHW	
QLD - Remote and rural Indigenous communities vs QLD population			
Risk of bias	*Very serious concerns*	Age, socioeconomic status/education, screening behaviours, geography (rural/remote vs urban), period and differing life expectances were considered important confounders. For a single study reporting this outcome (Coory 2000), there were very serious concerns regarding confounding due to differences in socioeconomic status/education and life expectancy.	*VERY LOW*
Indirectness	*Serious concerns*	Results directly relevant however from over 25 years ago	
Imprecision	*No serious concerns*	Based on a standardised mortality rate ratio of 1.06 with 95% confidence interval of 0.39 to 2.32, in a population of 100,000 men, it is estimated that there will be 3 more (27 less, 59 more) prostate cancer deaths among Aboriginal men in rural and remote communities when compared with the general population. Using a MCID of 150 prostate cancer deaths over a 15-year period/100,000 and thresholds for moderate and large effects of 300 and 600 deaths/100,000, the absolute difference between the two groups was not clinically important, and its 95%CI did not cross any thresholds.	
Inconsistency	*Not Assessable*	Not assessable as only a single study.	
Publication bias	*Undetected*	Single study and financial conflict of interest not reported but unlikely as authors were from Queensland Health	

AIHW = Australian Institute of Health and Welfare; CI = confidence interval; MCID = minimal clinically important difference

4. Summary of findings

Table 7. *Summary of findings for the relative risk of prostate cancer mortality for Indigenous peoples of Australia*

Outcome (MCID)	*Time frame*	*Studies (N)*	*Participants (N)*	*Study results and measurements*	*Absolute effect estimates*				*Certainty of evidence (GRADE)*	*Plain text summary*
					Metric	*Comparator*	*Exposed (95% CI)*	*Difference (95% CI)*		
NSW, QLD, NT, WA and SA - Indigenous vs Non-Indigenous										
Prostate cancer mortality (50/100,000)	5 years	1	NR	SMRR: 0.97 (0.56, 1.69)	Prostate cancer deaths per 100,000	25.3	24.5 (14.2, 42.8)	1 fewer (11 fewer, 18 more)	Low[1]	In Australia Indigenous men may not be at higher risk of prostate cancer mortality when compared with non-Indigenous men
Clinically significant prostate cancer		0								No results found
QLD - Remote and rural Indigenous communities vs QLD population										
Prostate cancer mortality (150/100,000)	15 years	1	NR	SMR:1.06 (0.39, 2.32)	Prostate cancer deaths per 100,000	44.3	47.0 (17.3, 102.8)	3 more (27 fewer, 59 more)	Very low[2]	We are uncertain as to whether the risk of prostate cancer mortality is no different for Indigenous men in remote and rural Indigenous communities in Queensland when compared with the male population of Queensland.
Clinically significant prostate cancer		0								No results found

CI = confidence interval; MCID = minimally important difference; SMR = standardized mortality ratio; SMRR = standardized mortality rate ratio

[1] Downgraded by two levels due to very serious concerns re risk of bias

[2] Downgraded by three levels due to very serious concerns re risk of bias and serious concerns re indirectness

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Murad M, Mustafa R, Schunemann H, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med* 2017;22: 85-87.

ROBINS-E Development Group (Higgins J, Morgan R, Rooney A, Taylor K, Thayer K, Silva R, Lemeris C, Akl A, Arroyave W, Bateson T, Berkman N, Demers P, Forastiere F, Glenn B, Hróbjartsson A, Kirrane E, LaKind J, Luben T, Lunn R, McAleenan A, McGuinness L, Meerpohl J, Mehta S, Nachman R, Obbagy J, O'Connor A, Radke E, Savović J, Schubauer-Berigan M, Schwingl P, Schunemann H, Shea B, Steenland K, Stewart T, Straif K, Tilling K, Verbeek V, Vermeulen R, Viswanathan M, Zahm S, Sterne J). Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E). Launch version, 20 June 2023. Available from: https://www.riskofbias.info/welcome/robins-e-tool.

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APPENDICES

Appendix A: Literature search strategy

Databases: Medline and Embase databases (via Ovid platform)

#	Searches
1	(prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or metast* or adeno*)).tw.
2	(aborigin* or torres* strait* island*).tw.
3	indigenous.mp.
4	2 or 3
5	1 and 4

Appendix B: GRADE assessment of the certainty of the evidence

Ratings	***Definitions***
⨁⨁⨁⨁ High certainty	The panel is very confident that the true effect lies close to that of the estimate of the effect
⨁⨁⨁◯ Moderate certainty	The panel is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁◯◯ Low certainty	The panel's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁◯◯◯ Very low certainty	The panel has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Appendix C: Excluded Studies

Article	*DOI/Link*	*Reason for exclusion*
Adams 2013	https://doi.org/10.5694/mja12.10490	No relevant outcomes
AIHW 2011	https://doi.org/10.1111/j.1743-7563.2011.01502.x	Superseded
Anonymous 2013	https://doi.org/10.1111/ajco.12127	Superseded
Anonymous 2023	https://doi.org/10.1002/cncr.34812	Excluded publication type
AIHW 2015	https://doi.org/10.1111/ajco.12407	Superseded
Baker 2011	https://doi.org/10.1111/j.1743-7563.2011.01469.x	Excluded publication type
Bygrave 2021	https://doi.org/10.3390/ijerph18052422	No relevant outcomes
Carson 2015	https://doi.org/10.1111/bju.13077	Excluded publication type
Condon 2004	https://doi.org/10.5694/j.1326-5377.2004.tb06052.x	Superseded
Condon 2016	https://doi.org/10.5694/mja16.00588	No relevant outcomes
Dasgupta 2022	https://doi.org/10.1371/journal.pone.0273244	Excluded population
Gibberd 2015	https://doi.org/10.5694/mja14.00701	Excluded population
Hall 2004	https://doi.org/10.5694/j.1326-5377.2004.tb06234.x	Excluded population
Ivers 2019	https://doi.org/10.1111/ajr.12484	Excluded population
Koczwara 2020	https://onlinelibrary.wiley.com/doi/epdf/10.1111/ajco.13497	Excluded population
Koh 2008	https://doi.org/10.2349/biij.4.3.e30	Excluded population
Lee 2015	https://onlinelibrary.wiley.com/doi/epdf/10.1111/ajco.12432	Excluded population
Moore 2015	https://doi.org/10.1016/s1470-2045(15)00232-6	No relevant outcomes
Oliveras 2023	http://dx.doi.org/10.1093/ndt/gfad063c_6346	Excluded population
Rodger 2012	https://onlinelibrary.wiley.com/doi/epdf/10.1111/ajco.12030	Excluded population
Rodger 2015	https://doi.org/10.1111/bju.12899	Excluded population
Roder 2009	https://pubmed.ncbi.nlm.nih.gov/20104959/	No relevant outcomes
Roseleur 2023	https://doi.org/10.1007/s00520-023-08146-y	Excluded population
Smith 2013	https://bjui-journals.onlinelibrary.wiley.com/doi/epdf/10.1111/bju.12292	Excluded population
Tervonen 2017	https://doi.org/10.1186/s12885-017-3374-6	Excluded population
Tervonen 2019	https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-019-0884-8	No relevant outcomes
Yu 2015	https://onlinelibrary.wiley.com/doi/epdf/10.1111/ajco.12376	Excluded population

AIHW = Australian Institute of Health and Welfare

3.4 Clinical question 4 – Digital Rectal Examination (DRE)

Clinical Question: *How best can digital rectal examination (DRE) be used, if at all, in association with prostate specific antigen (PSA) testing in the primary care setting?*

Systematic review report: The incremental value of performing a DRE in addition to PSA testing to detect clinically significant prostate cancer.

Authors

Rehana Abdus Salam, Suzanne Hughes, Susan Yuill, Michael David

Introduction

This review is an update of the previous systematic review undertaken for the 2016 guidelines. Since 2016 clinical interest has shifted from any prostate cancer to clinically significant prostate cancer to reduce harms associated with overdiagnosis, and reference standards for diagnostic accuracy studies have improved, therefore the previous selection criteria were narrowed to include:

- detection of clinically significant disease only; and
- reference standard biopsy of at least 8 cores unless all men undergo biopsy regardless of PSA levels or DRE results.

Evidence for an incremental benefit using a total PSA threshold of 3.0 ng/ml was considered directly relevant to the clinical question as the current guidelines recommend a total PSA threshold of 3.0 ng/ml.

PICO

This systematic review addresses the following PICO which is summarised in detail in Table 1.

For individuals at risk of prostate cancer without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what is the incremental value of performing a DRE in addition to PSA testing in detecting clinically significant cancer?

Table 1. *PICO components*

Population	***Index test 1***	***Index test 2***	***Reference standard***	***Outcomes***
Individuals at risk of prostate cancer without a history of prostate cancer or symptoms that might indicate prostate cancer	PSA and DRE tests	PSA test only	Prostate biopsy	Clinically significant prostate cancer • additional false positives per additional true positive detected (ΔFP/ΔTP) • Relative sensitivity and relative specificity Overall and by risk groups

ΔFP/ΔTP = difference in false positives/difference in true positives

1. Methods

1.1 Revised selection criteria

Table 2. *Selection criteria*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Diagnostic performance	
Study design	Paired diagnostic study	
Population	Individuals at risk of prostate cancer without a history of prostate cancer or symptoms that indicate prostate cancer who have undergone PSA test, DRE and prostate biopsy	Restricted only to symptomatic individuals Includes individuals who did not undergo biopsy
Index test 1	PSA (thresholds ≤ 4 ng/ml or age-specific thresholds) and DRE tests	PSA threshold > 4 ng/ml^
Index test 2	PSA (thresholds ≤ 4 ng/ml or age-specific thresholds) test only	PSA threshold > 4 ng/ml^
Reference standard	Prostate biopsy (adequate biopsy pre-specified as ≥ 8-core biopsy* unless all men undergo biopsy regardless of PSA levels or DRE results)	
Indications for biopsy	No indications for biopsy - all individuals underwent biopsy regardless of PSA level or results of any other test or PSA test result is one of the indications for biopsy and DRE result is another indication for biopsy Any definition of abnormal DRE and PSA threshold ≤ 4 ng/ml	Individuals selected for biopsy but indications for biopsy not reported
Outcomes	Clinically significant prostate cancer • Additional false positives per additional true positive detected (ΔFP/ΔTP) relative to PSA test alone** • Relative sensitivity and relative specificity Overall and by risk groups	Any prostate cancer Sensitivity and specificity where not all test negative men undergo biopsy
Language	English	
Publication period	2014 onwards (for update) 1990 - 2014 (original 2016 systematic review)	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data

ΔFP/ΔTP = difference in false positives/difference in true positives

* For this systematic review an adequate biopsy was pre-specified as ≥ 8-core biopsy. For studies published after 2014, biopsy was assumed to be adequate i.e. at least 8-core unless stated otherwise.

** Verification bias is a major issue when assessing the diagnostic performance of tests for prostate cancer as men normally do not undergo biopsy unless they are test positive. As a result, most studies examining diagnostic performance of adding DRE test to PSA testing are only able to report numbers of true positives and false positives. Where there is a comparison of two index tests in the same patient and where one index test is purely adding additional test positives to another index test, as when DRE is added to PSA testing, this data can be used to calculate the difference in true positives and the difference in false positives and the number of additional false positives for each additional cancer detected; findings that will not be subject to verification bias.

^ Evidence for an incremental benefit using a total PSA threshold of 3.0 ng/ml was considered directly relevant to the clinical question as the current guidelines recommend a total PSA threshold of 3.0 ng/ml. However, studies using a total PSA threshold of up to 4.0 ng/ml were also included as the day-to-day biological variability in a man's PSA level of 15%

means that, for a man with an average level of 3.0 ng/ml, the levels on consecutive days can be as high as 3.9 ng/ml (upper 95th percentile).

1.2 Definitions and terminologies

For the purpose of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Clinically significant prostate cancer refers to International Society of Urological Pathology (ISUP) grade ≥ 2.

False negative refers to individuals with the outcome of interest who were index test negative.

False positive refers to individuals who did not have the outcome of interest who were index test positive.

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).

Sensitivity refers to the proportion of true positives among those with clinically significant prostate cancer on biopsy (true positives plus false negatives)

Specificity refers to the proportion of true negatives among those without clinically significant prostate cancer on biopsy (false positives plus true negatives)

True negative refers to individuals who did not have the outcome of interest who were index test negative.

True positive refers to individuals with the outcome of interest who were index test positive.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website

- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- *Urological Society of Australia and New Zealand (USANZ) website*
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines) i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and be published from 2014 onwards. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

For the 2016 guidelines systematic review, Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 1990 using text terms and, where available, database-specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was coupled with a search for prostate-specific antigen (PSA) and digital rectal examination (DRE). To identify studies which considered Aboriginal and Torres Strait Islander peoples these searches were then coupled with search terms for Aboriginal and Torres Strait Islander peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published

after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

For the 2024 update of this systematic review, we searched Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase via the Ovid platform on 19th December 2023 using the Medline search strategy used for the 2016 guidelines systematic review. Searches were limited to articles published in English from 1st January 2014 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st September 2024. A complete list of the terms used in the search is included as Appendix A. The Cochrane Database of Systematic Reviews was searched on 13th March 2024 using the search term “prostate”. These searches were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction

Data was extracted from studies identified from the original 2016 systematic review and the 2024 search update that met the revised selection criteria. The following data was extracted from included studies by one reviewer, and checked by a second reviewer: Country and year of publication, study design, participant eligibility and age, study setting, sample size, details of index tests (DRE and PSA), details of reference test (indications for biopsy, type of biopsy and timing between index and reference tests), relevant outcomes reported (true positives (TP) and false positives (FP), differences in TPs and FPs, and for studies in which all men underwent biopsy regardless of test result, TPs, FPs, true negatives (TN) and false negatives (FN)), subgroup data, if available, and additional information including notable study limitations. Any differences in extracted data were resolved by discussion or by a third reviewer. Sensitivity and specificity were calculated using extracted TPs and FNs, and TNs and FPs respectively.

1.6 Meta-analyses

Ratios representing the change in false positive compared to the change in true positive events were pooled using the DerSimonian Laird random effects method (DerSimonian and Laird, 1986). In order to improve normality and stabilise the variance of estimates (Borenstein et al., 2021), prior to pooling, ratios were logarithmically transformed and then re-transformed following pooling using the Stata command *eform*. All p-values are two-sided, and statistical significance was set at 0.05. Forest plots were obtained to present the results graphically. The *metadta* command in Stata Version 18.0 (StataCorp 2023) was used to generate estimates of relative sensitivity and specificity, with their respective 95% confidence intervals for the two index tests. All analyses were conducted using Stata Version 18.0 (StataCorp 2023).

1.7 Risk of bias assessment

Two review authors independently evaluated the risk of bias in included studies using the Quality of Diagnostic Accuracy Studies-Comparative (QUADAS-C) tool (Yang 2021) (available at https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-c/). This tool is designed to assess the risk of bias in studies comparing the diagnostic accuracy of two different tests. It assesses the four sources of bias, patient selection, index test, reference standard, and flow and timing, included in the QUADAS-2 tool plus sources of bias arising from test comparisons.

1.8 GRADE assessment of certainty of evidence

A GRADE approach was used to assess the certainty of the body of evidence for the number of additional unnecessary further investigations per additional clinically significant cancer detected by digital rectal examination (DRE) for men with a normal PSA level, and the relative sensitivity and specificity of using DRE as well as PSA testing to detect clinically significant disease (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk bias of bias due to inadequate reference standard, indirectness of the results, imprecision, inconsistency or heterogeneity of the results and publication bias following GRADE guidance provided by Schunemann 2020a, Schunemann 2020b and Schunemann 2022. If required imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects determined following GRADE guidance provided by Schunemann 2022. Inconsistency was assessed based on the p statistic, the range of point estimates and a consideration of possible sources of heterogeneity. Potential publication bias (or small study effects) was assessed for meta-analyses with 10 or more studies using the nonparametric “trim and fill” method (Duval 2000) implemented using the STATA command *metatrim*, following guidance provided by Schunemann 2020b; where there were less than 10 studies, potential conflicts of interest were considered.

As per GRADE guidance, studies started with a high level of certainty in the evidence and were downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

Definitions of the GRADE ratings of certainty are presented in Appendix B.

2. Results

2.1 Guideline searches

Three potentially relevant guidelines were identified which were reportedly based on systematic reviews of the literature published from 2014 onwards. They were not considered for adoption; for all three guidelines the systematic reviews of the evidence were not accessible, and for two of the guidelines, risk of bias and GRADE assessments were not mentioned in the reported systematic review methods. (Appendix C).

2.2 Literature searches

Figure 1 outlines process of inclusion and exclusion of articles from the previous and updated systematic review. For this update, the combined search of Medline and Embase retrieved 3720 records after removal of

duplicates. Titles and abstracts were examined by one reviewer and 67 articles were retrieved for a more detailed evaluation. An additional two potentially relevant articles were identified from reference lists for a more detailed evaluation. Two reviewers independently assessed the full texts. Three articles from the 2025 update and one article from the previous 2016 systematic review met the revised selection criteria, totalling four articles eligible for inclusion. There were no studies that included of Aboriginal and/or Torres Strait Islander peoples that met the selection criteria. The retrieved articles that were not included in the previous review and this update along with the reasons for their exclusion are documented in Appendices D and E. The main reasons for exclusion were no relevant index tests and excluded study design.

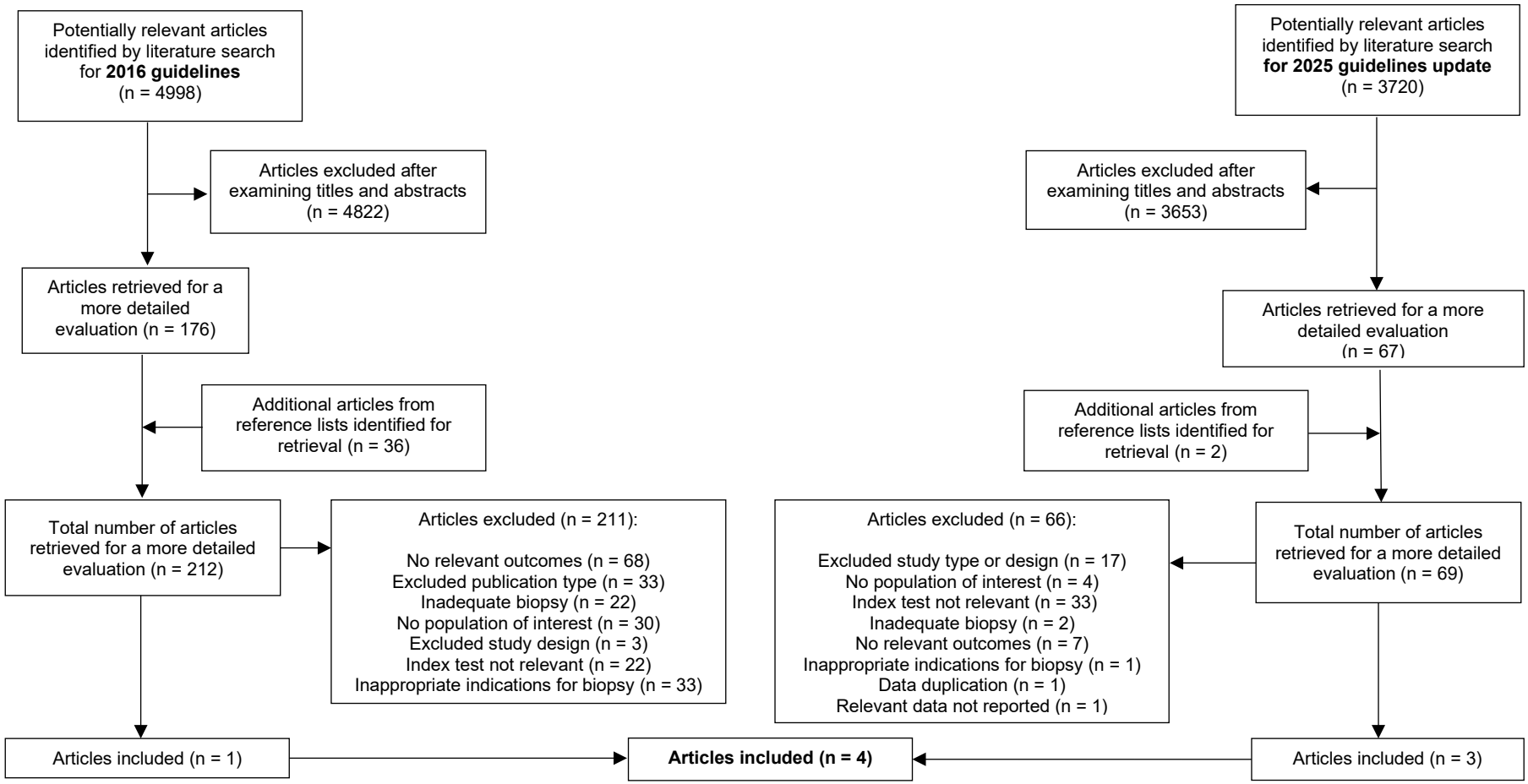

Figure 1. *Process of inclusion and exclusion of articles published from previous and updated systematic reviews*

2.3 Characteristics of included studies

The characteristics of studies included in the systematic review are described in Table 3.

Table 3. *Study characteristics of included studies reporting the incremental value of DRE in addition to PSA testing to detect clinically significant prostate cancer*

Study	*Design*	*Participants*	*Indications for biopsy*	*DRE*	*PSA test*	*Biopsy*	*Outcomes*	*Comments*
Screening population, biopsy regardless of PSA and DRE results								
Thompson 2007 (USA) *Prostate Cancer Prevention Trial (PCPT)*	Fully paired diagnostic study	Participants in PCPT **aged ≥ 55** years (median 63.2 years) with PSA ≤3 ng/ml, normal DRE, AUA symptom score <20, **at enrolment** (1994 - 1997) (N = 9,459) who underwent biopsy Assigned to placebo arm N = 5,947 (62.9%) N = 5,101 (analysed) Age: NR Asymptomatic: at enrolment Biopsy naïve: < 100% Race/ethnicity: > 90% white PSA ≤ 4.0ng/ml N = 4,551 PSA ≤ 4.0ng/ml + abnormal DRE N = 451 DRE positive GS ≥ 7 prevalence = 8.0%	PSA > 4.0 ng/ml or abnormal DRE at 7 annual screens then regardless of PSA level or DRE after 7 years follow-up Re-biopsy if DRE abnormal during subsequent years or PSA 1.5 times above level that prompted initial biopsy, or >10.0 ng/ml (most recent biopsy data analysed)	Normal or abnormal (details NR) Undertaken at 221 sites	Tandem E assay (1993-2000), Access assay (2000-2003) Performed in central laboratory	Within 1 year of PSA test and DRE Sextant biopsy recommended Details NR Reviewed by a central pathology laboratory and by pathologists at the study site	GS ≥ 7 (highly likely pre 2005 ISUP grades) *True positives* *False positive* *Sensitivity* *Specificity*	Pre-screened cohort Annual screening with PSA and DRE for up to 7 years Biopsies rarely prompted by both PSA and DRE Supported by National Cancer Institute grants COI NR
Biopsy of test-positive men only								

Study	*Design*	*Participants*	*Indications for biopsy*	*DRE*	*PSA test*	*Biopsy*	*Outcomes*	*Comments*
Busetto 2021 (Italy)	Fully paired diagnostic study	Men who underwent prostate biopsy (2018 – 2019) at a single centre (Policlinico Umberto Hospital?) N = 52 Mean (SD) age: 64 (8.7) years Asymptomatic: NR Biopsy naïve: 100% Race/ethnicity: NR PSA < 3ng/ml + abnormal DRE N = 4 DRE positive ISUP ≥ 2 prevalence = 0%	PSA ≥ 3 ng/ml (confirmed) or abnormal/ suspicious DRE	Not suspicious or suspicious (details NR) Undertaken at a hospital	NR	12-core TRUS-guided systematic biopsy +/- targeted biopsy (2 cores per lesion) if PI-RADS score 3-5 on mpMRI Performed by radiologist with >20 years of experience Samples evaluated by genitourinary pathologist with >10 years' experience	ISUP ≥ 2 (GS ≥ 7) *True positives* *False positive*	Unclear if men asymptomatic or symptomatic Referral population as data only for men undergoing biopsy for specific indications Declared no direct funding or COIs
Lee 2015 (Singapore)	Fully paired diagnostic study	Men who underwent prostate biopsy (2012 - 2014) at a single tertiary hospital (Tan Tock Seng Hospital?) N = 804 Mean (SD) age: 68.2 (8.9) years Asymptomatic: NR Biopsy naïve: 100% Race/ethnicity: 91.2% Chinese PSA < 4.0ng/ml + abnormal DRE N = 42 DRE positive GS ≥ 7 prevalence = 4.8%	PSA ≥ 4 ng/mL or DRE findings suspicious for malignancy	Normal or suspicious DRE findings suspicious for malignancy included induration, irregularity, nodularity and asymmetry Undertaken at a tertiary institution by urologists and urology trainees	PSA Hybritech Assay	12- or 18-core TRUS-guided biopsy Samples evaluated by pathologists at the same institution	GS ≥ 7 *True positives* *False positive*	Unclear if men asymptomatic or symptomatic Only the latest PSA results prior to prostate biopsy were used in analysis Referral population as data only for men undergoing biopsy for specific indications Funding NR Declared no COIs
Walsh 2014 (Ireland)	Fully paired diagnostic study	Men **with a normal age-specific PSA at referral** who underwent prostate biopsy (2009 - 2013) at Rapid Access Prostate Clinic (RAPC) in a single tertiary referral centre (St James Hospital?)	For men with normal PSA (primarily age-specific threshold (details NR) but may include some normal age specific PSA and PSA > 4.0 ng/mL),	Normal or abnormal (details NR) undertaken firstly by general practitioners and	NR	TRUS-guided biopsy Number of cores NR Samples evaluated by two consultant	GS ≥ 7 *True positives* *False positive*	Unclear if men asymptomatic or symptomatic

Study	Design	Participants	Indications for biopsy	DRE	PSA test	Biopsy	Outcomes	Comments
		N = 103 Mean (range) age = 63.3 (45-80) years Biopsy naïve: NR Asymptomatic: NR Race/ethnicity: NR PSA in normal age-specific range + abnormal DRE N = 74 (primary care setting) DRE positive GS ≥ 7 prevalence = 29.7% N = 60 (specialist setting) DRE positive GS ≥ 7 prevalence = 36.7%	abnormal DRE detected by urologist, family history, abnormal PSA kinetics, other? Men were assessed in an outpatient setting initially, where a decision was made by a consultant urologist as to whether biopsy was required	subsequently by urologists		pathologists at the same institution		74/103 abnormal DRE detected in primary care 60/103 abnormal DRE detected by urologist Referral population as data only for men undergoing biopsy for specific indications Declared no direct funding and no competing interests

COI = conflict of interest; DRE = digital rectal examination; GS = Gleason score; IQR = interquartile range; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; N = number; NR = not reported; PI-RADS = Prostate Image-Reporting and Data System; PSA = prostate specific antigen; SD = standard deviation; TRUS = transrectal ultrasound

2.4 Results by outcome of interest

Results for the detection of Gleason score ≥ 7 prostate cancer: results for individual studies are shown in Table 4 and for meta-analyses in Table 5 and Figures 2 and 3

Individual studies

Table 4. *Results of studies reporting the incremental value of DRE in addition to PSA testing with respect to detection of Gleason score ≥ 7 cancer*

Biopsy indication	*Screen positives biopsied (N)*	*TP (N)*	*FP (N)*	*ΔFP/ΔTP*	*PPV*	*Screen negatives biopsied (N)*	*FN (N)*	*TN (N)*	*Sensitivity (%)*	*Specificity (%)*	*Relative sensitivity (95%CI)*	*Relative specificity (95%CI%)*
Screening population, biopsy regardless of PSA and DRE results												
Thompson 2007 (PCPT)	N = 5,101 (placebo arm) PSA negative and abnormal DRE N = 451					**PSA threshold 4.0 ng/ml**				7 years of annual screening		
PSA >4.0	557	94	463		16.9	4,544	146	4,398	39.2	90.5		
PSA >4.0 and/or DRE+	1,006	130	876	11.47 (413/36)	12.9	4,095	110	3,985	54.2	82.0	1.38 (1.14-1.68)	0.91 (0.89-0.92)
Referral population, biopsy of test-positive men only												
Walsh 2014	PSA negative and GP detected abnormal DRE N = 74					**Age-related PSA threshold in > 90% instances**						
PSA > age-related threshold or < age-related threshold and > 4.0 ng/ml	NR	NR	NR		NR	NA	NA	NA	NA	NA	NA	NA
PSA > age-related threshold or < age-related threshold and DRE+ (GP assessed DRE)	NR	NR	NR	2.36 (52/22)	NR	NA	NA	NA	NA	NA	NA	NA
PSA > age-related threshold or < age-related threshold and DRE+ (urologist assessed DRE)	NR	NR	NR	1.73 (38/22)	NR	NA	NA	NA	NA	NA	NA	NA
Lee 2015	PSA negative and abnormal DRE N = 42					**PSA threshold 4.0 ng/ml**						
PSA ≥ 4	762	213	549		28.0	NA	NA	NA	NA	NA	NA	NA
PSA ≥ 4 or DRE+	804	215	589	20 (40/2)	26.7	NA	NA	NA	NA	NA	NA	NA

Busetto 2021	PSA negative and abnormal DRE N = 4				**PSA threshold 3.0 ng/ml**							
PSA ≥ 3	48	7	41		14.6	NA	NA	NA	NA	NA	NA	NA
PSA ≥ 3 or DRE+	52	7	45	4/0	13.5	NA	NA	NA	NA	NA	NA	NA

+ = positive; ΔFP/ΔTP = difference in false positives/difference in true positives; CI = confidence interval; DRE = digital rectal examination; FP = false positive; FN = false negative; NA = not applicable; N = number; NR = not reported; PSA = prostate specific antigen; TN = true negative; TP = true positive

Meta-analyses

Table 5. *Results of meta-analyses of studies reporting the incremental value of DRE in addition to PSA testing with respect to detection of Gleason score ≥ 7 cancer*

Analysis	***Figure***	***Studies (N)***	***Participants** with normal PSA level and abnormal DRE **(N)***	***PSA threshold***	***DRE setting***	**ΔFP/ΔTP (95%CI)**	***Heterogeneity p-value***
Meta-analysis	2	3	567	4.0 ng/ml or age-related	Primary care: 1 study Secondary or tertiary care: 1 study Unknown: 1 study	7.46 (2.08-26.74)	< 0.001
Meta-analysis*	3	3	553	4.0 ng/ml or age-related	Secondary or tertiary care: 2 studies Unknown: 1 study	6.83 (1.52-30.61)	< 0.001
Single study	NA	1	4	3.0 ng/ml	Secondary or tertiary care	80.00 (4.92-1301.28)	NA

ΔFP/ΔTP = difference in false positives/difference in true positives; CI = confidence interval; DRE = digital rectal examination; N = number; NA = not applicable; PSA = prostate specific antigen

* Sensitivity analysis substituting Walsh 2014 results for GP performed DRE with Walsh 2014 results for urologist performed DRE

Figures

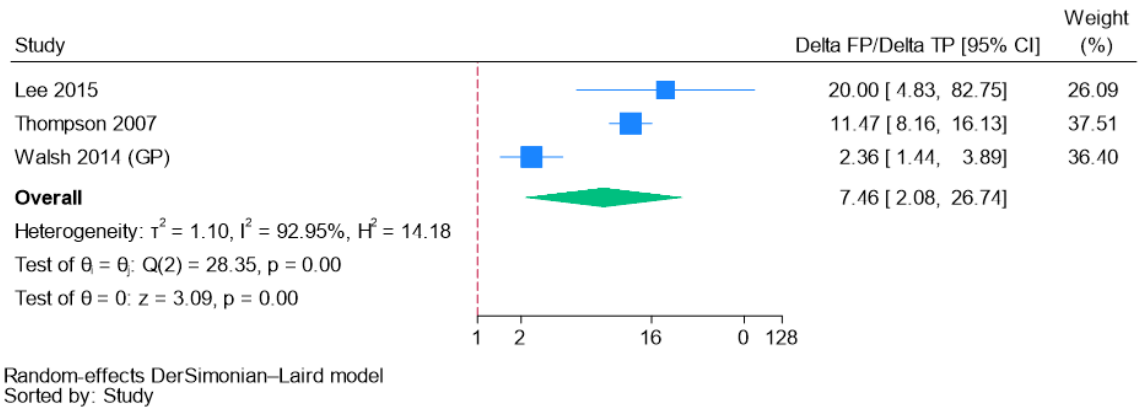

Figure 2. *Incremental value of DRE meta-analysis for PSA threshold of 4.0 ng/ml or age-related PSA threshold (Walsh 2014 general practitioner performed DRE)*

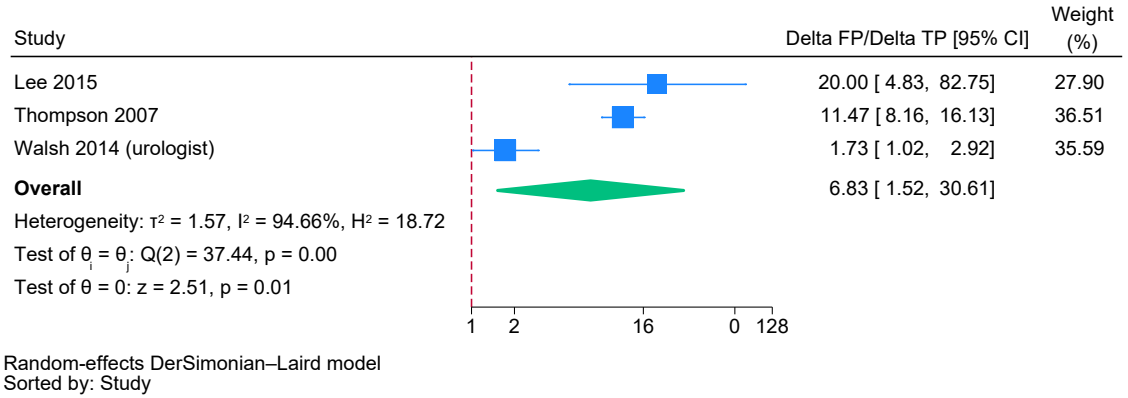

Figure 3. *Sensitivity Analysis: Incremental value of DRE meta-analysis for PSA threshold of 4.0 ng/ml or age-related threshold (Walsh 2014 urologist performed DRE)*

2.5 Risk of bias

Assessment of risk of bias of included studies is described in Table 6.

Table 6. *Risk of bias assessments for included studies using the Quality of Diagnostic Accuracy Studies-Comparative (QUADAS-C) tool*

Study	Test	Risk of bias (for each index test)				Risk of bias (for comparison of index tests)				Overall
		Patient selection	Index test	Reference standard [a]	Flow and Timing [b]	Patient selection	Index test	Reference standard [a.]	Flow and Timing [b]	
Busetto 2021	PSA test	Low	Low	High	High	Low	High	High	High	**High**
	DRE	Low	Moderate	High	High					
Lee 2015	PSA test	Low	Low	High	High	Low	High	High	High	**High**
	DRE	Low	Low	High	High					
Thompson 2007	PSA test	Low	Low	High	High	Low	High	High	High	**High**
	DRE	Low	Moderate	High	High					
Walsh 2014	PSA test	Specialist: Low	Low	High	Specialist: Low	Specialist: Low	High	High	Specialist: Low	**High**
	DRE	Specialist: Low	Moderate	High	Specialist: Low					
	PSA test	GP Low	Low	High	High	GP: Moderate	High	High	High	**High**
	DRE	GP: Moderate	Moderate	High	High					

[a.] *An adequate biopsy was pre-specified as 20 or more cores*
[b.] *An appropriate interval was pre-specified as up to 3 months*

Key to overall rating
Low risk of bias: A study that received "low" for all domains
High risk of bias: Received "high" for one or more domains

3. GRADE assessment of certainty of evidence

Additional false positives per additional ISUP Grade ≥ 2 prostate cancer detected with digital rectal examination (DRE) – assessments are shown in Table 7

Sensitivity and specificity of digital rectal examination (DRE) to detect ISUP Grade ≥ 2 prostate cancer in PSA test negative populations – assessments are shown in Table 8

Table 7. *GRADE assessment of the certainty of the evidence for the number of additional false positives per additional ISUP Grade ≥ 2 prostate cancer detected if use digital rectal examination (DRE) as well as PSA testing to detect ISUP Grade ≥ 2 prostate cancer in the primary care setting*

GRADE domain	*Rating*	*Reason for downgrading*	*Certainty of evidence*
PSA threshold 3.0 ng/ml			
Risk of bias	Serious concerns (-1)	Single study (Busetto 2021) at high risk of bias due to inadequate reference standard.	**Very low**
Indirectness	Very serious concerns (-2)	Did not report whether patients asymptomatic or symptomatic at biopsy. DRE undertaken in hospital setting rather than primary care setting - likely diagnostic expertise was different from that in the primary care setting.	
Imprecision	Extremely serious concern (-3)	Only 4 individuals with PSA < 3.0 ng/ml and an abnormal DRE i.e. N = 4. The estimated number of additional false positives per additional ISUP Grade ≥ 2 prostate cancer was 80.00 with a 95%CI of 4.92-1301.28	
Inconsistency	Not assessed	Single study	
Publication bias	Not detected	Authors declared no direct funding or conflicts of interest.	
PSA threshold 4.0 ng/ml			
Risk of bias	Serious concerns (-1)	All 3 studies at high risk of bias due to inadequate reference standard.	**Very low**
Indirectness	Very serious concerns (-2)	Two of the three studies (Walsh 2014, Lee 2015) did not report whether patients asymptomatic or symptomatic at biopsy. The third study included men who were asymptomatic at biopsy but the proportion of men that were asymptomatic at biopsy was not reported. All three studies used a PSA threshold of 4.0 rather than 3.0 ng/ml. In one of the three studies the DRE was undertaken in a specialist setting rather than primary care setting (Lee 2015) and one of the other studies reported a higher ratio in the primary care setting than the specialist setting (Walsh 2014) supporting the assumption that the ratio will vary with diagnostic expertise. One of the three studies used Gleason scores that were highly likely determined prior to 2005 (Thompson 2007) when Gleason score categories were defined differently.	
Imprecision	Not assessed	The estimated number of additional false positives per additional ISUP Grade ≥ 2 prostate cancer was 7.46 with a 95%CI of 2.08-26.74. **This outcome metric is dependent on the prevalence of ISUP Grade ≥ 2 prostate cancer amongst PSA negative individuals**. Imprecision was not assessed as the certainty of the evidence was already very low based on risk of bias and indirectness and inconsistency of the evidence.	
Inconsistency	Serious concerns	The p for heterogeneity was < 0.001 and remained so when urologist results were used instead of general practitioner results in a sensitivity analysis. Point estimates ranged from 2.36 in a population in a primary	

		care setting (Walsh 2014, point estimate even lower in tertiary setting) to 20 in a primarily Chinese population in a hospital setting (Lee 2015). The point estimate of 20 could be explained by the much lower prevalence of ISUP Grade ≥ 2 prostate cancer in this population however the underlying prevalence of ISUP Grade ≥ 2 prostate cancer amongst PSA negative individuals in each of these studies is unknown.	
Publication bias	Not detected	All 3 studies either reported no direct funding by industry and/or declared no conflicts of interest.	

CI = confidence interval; DRE = digital rectal examination; ISUP = International Society of Urological Pathology; N = number; PSA = prostate specific antigen

Table 8. *GRADE assessment of the certainty of the evidence for the sensitivity and specificity of digital rectal examination (DRE) to detect ISUP Grade ≥ 2 prostate cancer in PSA test negative populations*

GRADE domain	***Rating***	***Reason for downgrading***	***Certainty of evidence***
PSA threshold 4.0 ng/ml			
Risk of bias	Serious concerns (-1)	Single study (Thompson 2007) at high risk of bias due to inadequate reference standard.	**Very low**
Indirectness	Serious concerns (-2)	This study used a PSA threshold of 4.0 rather than 3.0 ng/ml and used Gleason scores that were highly likely determined prior to 2005 (Thompson 2007) when Gleason score categories were defined differently.	
Imprecision	No serious concerns	If prevalence of ISUP Grade ≥ 2 prostate cancer is 10%, in a population of 1000 individuals, offering further investigations to men with an abnormal DRE as well as to men with a PSA level > 4.0 ng/ml is estimated to detect an additional 15 (5-27) Gleason score ≥ 7 prostate cancers and result in an additional 73 (65-90) unnecessary investigations. For additional Gleason score ≥ 7 prostate cancer detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI did not cross any thresholds For additional unnecessary investigations using a MCID of >100/1000 and thresholds for moderate and large effects of >200/1000 and >400/1000 the 95%CI did not cross any thresholds	
Inconsistency	Not assessed	Single study	
Publication bias	Not detected	Authors reported that the study was supported by National Cancer Institute grants	

CI = confidence interval; DRE = digital rectal examination; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; N = number; PSA = prostate specific antigen

4. Summary of findings

Table 9. *Summary of findings for the effect of using digital rectal examination (DRE) in addition to PSA testing to detect clinically significant prostate cancer if the prevalence amongst asymptomatic men of ISUP Grade ≥ 2 prostate cancer is 5% or 10% based on relative sensitivity and relative specificity estimates which are not prevalence dependent.*

Outcome	***Studies (Participants)***	***Control summary sensitivity***	***Control summary specificity***	***Relative sensitivity*** *(95% CI)*	***Relative specificity*** *(95% CI)*	***Implications in a population of 1000 asymptomatic men with a clinically significant prostate cancer prevalence^ of:***						***Certainty of the evidence (GRADE)***	***Plain text summary***
						5%		***10%***					Adding DRE to PSA testing to identify individuals for further investigations increases the number of clinically significant cancers detected and the number of unnecessary further investigations
						Additional csPrCas detected (95% CI)	*Additional unnecessary further investigations (95% CI)*	Estimated ΔFP/ ΔTP	*Additional csPrCas detected (95% CI)*	*Additional unnecessary further investigations (95% CI)*	Estimated ΔFP/ ΔTP		
Test positive threshold comparison: *PSA > 4.0 ng/ml* ***or abnormal DRE*** *vs PSA > 4.0 ng/ml*													
ISUP Grade ≥ 2	*1 (5,101)*	*0.392*	*0.905*	*1.38 (1.14, 1.68)*	*0.91 (0.89, 0.92)*	*7 (3, 13)*	*77 (69, 95)*	*11.0*	*15 (5, 27)*	*73 (65, 90)*	*4.9*	*Very low*[a]	If DRE is added to PSA testing, we are uncertain as to whether the increases in clinically significant prostate cancer detection and additional unnecessary further investigations are clinically unimportant for asymptomatic individuals if a PSA threshold of 3.0 ng/ml is used ** # For asymptomatic individuals in the primary care setting, we are uncertain as to the number of additional unnecessary further investigations to detect an additional clinically significant prostate cancer when DRE is used in addition to PSA testing with a PSA threshold of 3.0ng/ml and the prevalence of clinically significant disease is 5% or 10%

ΔFP/ΔTP = number of additional unnecessary further investigations per additional clinically significant cancer detected; CI = confidence interval; DRE = digital rectal examination; csPrCa = clinically significant prostate cancer; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; PSA = prostate specific antigen

Additional clinically significant cancers detected are the number of additional ISUP grade ≥ 2 prostate cancers detected if DRE is used in addition to PSA testing to identify individuals for further investigations; this is a desirable outcome of using in DRE in addition to PSA testing to identify individuals for further investigations.

Additional unnecessary further investigations are the number of additional unnecessary further investigations if DRE is used in addition to PSA testing to identify individuals for further investigations; this is a non-desirable outcome of using DRE in addition to PSA testing to identify individuals for further investigations.

^ Implications are calculated for prevalences of ISUP Grade ≥ 2 of 5% and 10% as there are no data on the prevalence of ISUP Grade ≥ 2 in populations of asymptomatic individuals in Australia.

*** Using thresholds of 50, 100 and 200 additional ISUP Grade ≥ 2 prostate cancer/1000 for small (MCID), moderate and large effects*

 # Using thresholds of >100, >200 and >400 unnecessary further investigations (including mpMRI triage) /1000 for small (MCID), moderate and large effects

[a] *Serious concerns re bias due to inadequate reference standard and very serious concerns re indirectness as results were reported for a PSA threshold of 4.0 not 3.0 ng/ml and the Gleason scores were highly likely to have been determined prior to 2005 when criteria for Gleason scores were revised.*

Table 10. *Summary of findings for the effect of using digital rectal examination (DRE) in addition to PSA testing to detect clinically significant prostate cancer based on reported increases in clinically significant prostate cancer detected and further investigations.*

Outcome	***Studies (Participants with normal PSA and abnormal/ suspicious DRE)***	***Setting***	***Observed ΔFP/ΔTP (95%CI)***	***Certainty of the evidence (GRADE)***	***Plain text summary***
Number of additional unnecessary further investigations per additional clinically significant prostate cancer detected for individuals with **PSA < 3.0 ng/ml**	1 (4)	Hospital	80.0 (4.9, 1,301.3)	Very low[a]	The observed number of additional unnecessary further investigations to detect an additional clinically significant cancer is dependent on the prevalence of clinically significant prostate cancer. For asymptomatic individuals in the primary care setting, we are uncertain as to the number of additional unnecessary further investigations to detect an additional clinically significant prostate cancer when DRE is used in addition to PSA testing with a threshold of 3.0ng/ml.
Number of additional unnecessary further investigations per additional clinically significant prostate cancer detected for individuals with **PSA < 4.0 ng/ml**	3 (567)	Primary care, tertiary institution or not reported	7.46 (2.08, 26.74)	Very low[b]	The observed number of additional unnecessary further investigations to detect an additional clinically significant cancer is dependent on the prevalence of clinically significant prostate cancer. For asymptomatic individuals in the primary care setting, we are uncertain as to the number of additional unnecessary further investigations to detect an additional clinically significant prostate cancer when DRE is used in addition to PSA testing with a threshold of 3.0 ng/ml.

CI = confidence interval; csPrCa = clinically significant prostate cancer; DRE = digital rectal examination; PSA = prostate specific antigen

[a] *Serious concerns re bias due to inadequate reference standard, very serious concerns re indirectness as study undertaken in hospital not primary care setting and unclear whether participants symptomatic or asymptomatic and extremely serious concerns re imprecision*

[b] *Serious concerns re bias due to inadequate reference standard and inconsistency, very serious concerns re indirectness as results were reported for a PSA threshold of 4.0 not 3.0 ng/ml and unclear whether participants symptomatic or asymptomatic*

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APPENDICES

Appendix A: Literature search strategies

A.1 Search strategies used for the 2016 guidelines

Database: Medline

#	*Search terms*
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	(digital adj1 rectal adj1 exam$).mp.
5	(DRE or 'rectal exam$' or 'physical exam$' or palpabl$ or nonpalpabl$ or palpation or 'prostate exam$').mp.
6	Digital Rectal Examination/
7	(clinical$ adj2 (detect$ or diagnos$ or exam$)).mp.
8	4 or 5 or 6 or 7
9	('prostate specific antigen' or PSA).tw.
10	Prostate-Specific Antigen/
11	9 or 10
12	3 and 8 and 11
13	limit 12 to (english language and humans and yr="1990 -Current")

Search terms used to identify Aboriginal and Torres Strait Islander populations

1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

Database: Embase

#	*Search terms*
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
2	'prostate cancer'/exp
3	1 OR 2
4	'digital rectal examination' OR 'digital rectal exam' OR 'digital rectal examinations' OR 'digital rectal exams'
5	prostate NEAR/1 exam* OR rectal near/1 exam* OR physical near/1 exam OR dre OR palpabl* OR nonpalpabl* OR palpation OR impalpabl*
6	'digital rectal examination'/exp
7	(clinical OR clinically) NEAR/2 (detect* OR diagnos* OR exam*)
8	4 OR 5 OR 6 OR 7
9	'prostate specific antigen' OR psa
10	'prostate specific antigen'/exp

11	9 OR 10
12	3 AND 8 AND 11
13	12 NOT [medline]/lim AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1990-3000]/py

Search terms used to identify Aboriginal and Torres Strait Islander populations

#	***Search terms***
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

Database: Cochrane Database of Systematic Reviews – The Cochrane Library:

Title, abstracts, keywords: “prostate”

Databases: Database of Abstracts of Reviews of Effects and Health Technology Assessment (via OvidSP):

#	***Search terms***
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

A.2 Search strategy used for the 2025 guidelines update

Databases: Medline and Embase databases (via Ovid platform)

#	***Search terms***
1	(prostat$ adj4 (neoplas$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$ or metasta$)).tw.
2	exp Prostatic Neoplasms/
3	1 or 2
4	(digital adj1 rectal adj1 exam$).tw.
5	(DRE or 'rectal exam$' or 'physical exam$' or palpabl$ or nonpalpabl$ or palpation or 'prostate exam$').tw.
6	Digital Rectal Examination/
7	(clinical$ adj2 (detect$ or diagnos$ or exam$)).tw.
8	4 or 5 or 6 or 7
9	('prostate specific antigen' or PSA).tw.
10	Prostate-Specific Antigen/
11	9 or 10
12	3 and 8 and 11
13	limit 12 to english language
14	limit 13 to human
15	limit 14 to humans
16	limit 15 to yr="2014 -Current"
17	(conference abstract or conference review).pt.
18	16 not 17
19	remove duplicates from 18

Appendix B: GRADE assessment of the certainty of the evidence

Ratings	*Definitions*
⨁⨁⨁⨁ High certainty	The panel is very confident that the true effect lies close to that of the estimate of the effect
⨁⨁⨁◯ Moderate certainty	The panel is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁◯◯ Low certainty	The panel's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁◯◯◯ Very low certainty	The panel has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reportedly based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Systematic reviews of the evidence were not accessible.
British Columbia	https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines	Prostate Cancer Part 1: Diagnosis and Referral in Primary Care	2020	Systematic reviews of the evidence were not accessible and the reported systematic review methods did not mention risk of bias or GRADE assessments or the evidence to decision processes used.
Prostate Cancer Foundation USA	Garroway et al. 2024 https://www.doi.org/10.1056/EVIDoa2300289	Prostate Cancer Foundation Screening Guidelines for Black Men in the United States	2024	Systematic reviews of the evidence were not accessible and the reported systematic review methods did not mention risk of bias or GRADE assessments.

Appendix D: Excluded studies - 2016 guidelines systematic review

Study	*Reason for Exclusion*
Agalliu 2007	No relevant outcomes
Ahmed 2011	No relevant outcomes
Akdas 1995	No relevant outcomes (methods of calculating diagnostic outcomes unclear)
Al Rumaihi 2013	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Alibhai 2004	Narrative review/comment/letter to editor (no original data)
Allhoff 1993	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Altwein 1999	Not all men underwent both DRE and PSA
Andriole 2005	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Argyropoulos 2005	Inappropriate population
Arratia-Maqueo 2010	Not all men underwent both DRE and PSA
Aziz 1993	Narrative review/comment/letter to editor (no original data)
Babaian 1991 a	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Babaian 1991 b	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Babaian 1992	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Babaian 1993	Inappropriate population
Babaian 2001	Not all men underwent both DRE and PSA
Baden 2011	No relevant outcomes
Bangma 1995 a	No relevant outcomes
Bangma 1995 b	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Bangma 1995 c	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme

Bangma 1997	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Bare 1993	Inappropriate population
Basler 1998	Narrative review/comment/letter to editor (no original data)
Beemsterboer 1999	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Beemsterboer 2000	No relevant outcomes
Benson 1993	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Bentvelsen 1993	Narrative review/comment/letter to editor (no original data)
Berger 1993	Narrative review/comment/letter to editor (no original data)
Bergstralh 2007	Not all men underwent both DRE and PSA
Borden 2006	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Boulos 2001	No relevant outcomes (no number of additional FP reported)
Bozeman 2005	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Brett 1998	Not all men underwent both DRE and PSA
Bretton 1994	Inappropriate population (indication for biopsy unclear)
Bruno 2007	No relevant outcomes
Bunting 2002	Narrative review/comment/letter to editor (no original data)
Candas 2000	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Canto 2002	Narrative review/comment/letter to editor (no original data)
Carroll 2001	Narrative review/comment/letter to editor (no original data)
Carter 1997	No relevant outcomes
Carvalhal 1999	No relevant outcomes
Catalona 1991	Inappropriate population
Catalona 1993	No relevant outcomes (no separate data reported for DRE)
Catalona 1994	Inappropriate population (stratified results only reported for men who underwent prostatectomy)
Catalona 1997	No relevant outcomes
Chen 1996	No relevant outcomes
Chevil 2012	No relevant outcomes
Chong 2001	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Chu 1994	Narrative review/comment/letter to editor (no original data)
Chu 2011	No relevant outcomes
Chun 2006	No relevant outcomes
Clements 1997	Narrative review/comment/letter to editor (no original data)
Coley 1995	Narrative review/comment/letter to editor (no original data)
Coley 1997	Narrative review/comment/letter to editor (no original data)
Concato 2006	No relevant outcomes
Cooner 1993	Narrative review/comment/letter to editor (no original data)
Cooner 2002	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Crawford 1996	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Crawford 1999	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
DeAntoni 1997	Narrative review/comment/letter to editor (no original data)
Djulbegovic 2010	No relevant outcomes (systematic review)
Douville 1996	Narrative review/comment/letter to editor (no original data)
Drago 1992	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Ellis 1994	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Estham 1991	Inappropriate population
El-Galley 1995	Inappropriate population
Fiella 1996	Inappropriate population
Foo 2013	No relevant outcomes
Fowler 2000	Inadequate reference standard
Friedman 1991	Inappropriate study design
Galic 2003	No relevant outcomes
Gann 1995	No relevant outcomes
Gerber 1993	No relevant outcomes
Giri 2007	No relevant outcomes
Glass 2013	Narrative review/comment/letter to editor (no original data)
Gohji 1995	Inappropriate population
Gomez-Guerra 2009	Inadequate reference standard
Gore 2001	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)

Gosselaar 2007	Not all men underwent both DRE and PSA
Gosselaar 2008	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Gosselaar 2009	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Gretzer 2002	Narrative review/comment/letter to editor (no original data)
Grubb 2008	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Gustafsson 1992	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Haid 1994	Inappropriate population
Hamilton 2005	Inappropriate population
Hattangadi 2012	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Higashihara 1996	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Hoedmaeker 1997	Inappropriate population
Hoffman 2000	Not all men underwent both DRE and PSA (systematic review)
Hoogendam 1999	Not all men underwent both DRE and PSA (systematic review)
Hugosson 2003	No relevant outcomes
Imai 1994	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Imai 1995	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Issa 2006	Inappropriate population
Ito 2001	No relevant outcomes (no separate data for DRE)
Jacobsen 1998	Inappropriate study design
Karakiewicz 2005	No relevant outcomes (no separate data for DRE)
Kawakami 2008	Inappropriate population
Killian 1990	Narrative review/comment/letter to editor (no original data)
Kim 2011	Not all men underwent both DRE and PSA
Kirby 1994	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Kranse 1999	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Lane 2007	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Lee 1992	Narrative review/comment/letter to editor (no original data)
Liang 2011	No relevant outcomes
Lin 1998	No relevant outcomes
Littrup 1992	Narrative review/comment/letter to editor (no original data)
Littrup 1994	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Littrup 1995	Narrative review/comment/letter to editor (no original data)
Loeb 2006	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Loeb 2009	Narrative review/comment/letter to editor (no original data)
Lodding 1998	Not all men underwent both DRE and PSA
Lopez-Saez 2004	No relevant outcomes
Lopez-Saez 2007	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Louria 1992	Narrative review/comment/letter to editor (no original data)
Maattanen 1999	Not all men underwent both DRE and PSA
Maattanen 2007	Not all men underwent both DRE and PSA
Makinen 2001	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Marta 2013	Narrative review/comment/letter to editor (no original data)
Meeks 2009	Inappropriate population
Mettlin 1991	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Mettlin 1993 a	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Mettlin 1993 b	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Mettlin 1996	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Mettlin 1997	No relevant outcomes
Mistry 2003	No relevant outcomes
Mizusawa 2011	Inappropriate population
Mohamed 2013	Not all men underwent both DRE and PSA
Montironi 2000	Narrative review/comment/letter to editor (no original data)
Morgentaler 2006	Inappropriate population
Muris 1993	Not all men underwent both DRE and PSA (systematic review)
Nadler 2005	No relevant outcomes
Nam 2006	Inappropriate study design
Ng 2005	Inappropriate population
Ngo 2011	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)

Nightingale 1994	Narrative review/comment/letter to editor (no original data)
Nishio 2003	No relevant outcomes
Norming 1991	No relevant outcomes
Oesterling 1992	No relevant outcomes
Oesterling 1995	Inappropriate population
Ohori 1995	Inappropriate population
Ojewola 2012	No relevant outcomes
Okada 2010	No relevant outcomes
Okotie 2007	Inappropriate population (men who underwent prostatectomy)
Olson 1994	Not all men underwent both DRE and PSA
Ouzaid 2012	No relevant outcomes
Park 2011	No relevant outcome (no separate data for DRE)
Pedersen 1990	No relevant outcomes
Perrin 1991	Not all men underwent both DRE and PSA
Petrillo 2013	No relevant outcomes
Philip 2005	No relevant outcomes
Pinsky 2005	No relevant outcomes
Polascik 1999	Narrative review/comment/letter to editor (no original data)
Potter 2001	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Quinlan 2007	No relevant outcomes (no number of additional FP reported)
Reissigl 1996	No relevant outcomes
Reissigl 1997 a	No relevant outcomes
Reissigl 1997 b	Not all men underwent both DRE and PSA
Richie 1993	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Richie 1994	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Rietbergen 1997	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Roberts 2000	Inappropriate population
Roobol 2003	Narrative review/comment/letter to editor (no original data)
Roobol 2006	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Roobol 2011	Not all men underwent both DRE and PSA
Roobol 2012	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Rowe 2005	No relevant outcomes (no separate data for DRE)
Ryden 2007	Not all men underwent both DRE and PSA
Sandblom 2011	No relevant outcomes
Schmidt 1992	Narrative review/comment/letter to editor (no original data)
Schroder 1996	Inappropriate population
Schröder 1998	Inappropriate population (for outcome of cancer detection stratified by Gleason Score)
Schröder 2000	No relevant outcomes (no separate data for DRE)
Schröder 2001	No relevant outcomes (no separate data for DRE)
Schröder 2003	Narrative review/comment/letter to editor (no original data)
Selley 1997	Narrative review/comment/letter to editor (no original data)
Seo 2007	Inappropriate population
Shaida 2009	No relevant outcomes
Shapiro 1994	No relevant outcomes
Shigemura 2008	No relevant outcomes
Shim 2007	No relevant outcomes
Shimizu 1995	No relevant outcomes (no separate data for DRE)
Singh 2003	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Slawin 1995	Narrative review/comment/letter to editor (no original data)
Small 1993	Narrative review/comment/letter to editor (no original data)
Smith 1997	Inappropriate or unclear indications for biopsy (not all men positive on PSA and/or DRE underwent biopsy)
Song 2005	Inappropriate population
Spencer 1993	No relevant outcomes
Stenman 1994	No relevant outcomes
Stone 1994	Not all men underwent both DRE and PSA
Thompson 2004	More current data available (Thompson 2007 – included)
Thompson 2005	No relevant outcomes
Thompson 2006 a	No relevant outcomes

Thompson 2006 b	No relevant outcomes
Tornblom 1999	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Uchida 2000	Not all men underwent both DRE and PSA
Van Cangh 1996	No relevant outcomes
Van der Bergh 2008	No relevant outcomes
Van der Cruijsen-Koeter 2005	No relevant outcomes
Van der Cruijsen-Koeter 2011	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Van Vugt 2011	No relevant outcomes
Van Vugt 2012	No relevant outcomes
Vickers 2013	No relevant outcomes
Vis 2001	No relevant outcomes (no separate data for DRE)
Vis 2002	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Walz 2008	No relevant outcomes (no separate data for DRE)
Weinmann 2005	Not all men underwent both DRE and PSA
Yamamoto 1994	Inappropriate population
Yamamoto 2001	No stratification of cancers detected by e.g. Gleason score, inadequate biopsy scheme
Yu 1998	Inappropriate population

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Appendix E: Excluded studies - 2025 guidelines update

Author/Year	*DOI/Link*	*Reason for exclusion*
Akarasakul 2019	https://ir.swu.ac.th/jspui/handle/123456789/12349	No outcome of interest
Akman 2014	http://dx.doi.org/10.7314/APJCP.2014.15.20.8937	Index test not relevant
Al-Khalil 2016 a	http://dx.doi.org/10.2147/RRU.S117963	Index test not relevant
Al-Khalil 2016 b	https://doi.org/10.1007/s11255-015-1146-2	Index test not relevant
Allameh 2017	https://doi.org/10.5812/ijcm.7415	Index test not relevant
Alvarado Villavicencio 2022	https://doi.org/10.14704/NQ.2022.20.13.NQ88025	Data duplication
Amaya-Fragoso 2021	https://doi.org/10.1016/j.urolonc.2021.05.022	Index test not relevant
Andersson 2022	https://doi.org/10.1016/j.euros.2022.08.006	Index test not relevant
Ankerst 2014 a	https://doi.org/10.1016/j.urology.2014.02.035.	Index test not relevant
Ankerst 2014 b	https://doi.org/10.1007/s00345-012-0869-2	Index test not relevant
Ashorobi 2017	https://doi.org/10.1177/1557988315584794	No outcome of interest
Ankerst 2018	https://doi.org/10.1016/j.eururo.2018.05.003	Index test not relevant
Auffenberg 2017	http://dx.doi.org/10.1016/j.urology.2017.01.039	Index test not relevant
Bachour 2015	http://dx.doi.org/10.7314/APJCP.2015.16.14.5967	Index test not relevant
Bae 2020	https://doi.org/10.14366/usg.19036	Index test not relevant
Banez 2014	https://doi.org/10.1007/s00345-012-0919-9	Index test not relevant
Bhat 2019	https://doi.org/10.1016/j.urology.2018.12.010	Index test not relevant
Bhindi 2017	http://dx.doi.org/10.1016/j.urolonc.2017.06.044	Index test not relevant
Breza 2019	https://doi.org/10.4149/BLL_2019_054	Index test not relevant
Bruno 2021	https://doi.org/10.3389/fonc.2021.693684	Index test not relevant
Chiu 2016	https://doi.org/10.1007/s11255-016-1350-8	Index test not relevant
Chiu 2022	https://doi.org/10.1038/s41391-021-00429-x	Index test not relevant
Cormio 2018	https://doi.org/10.3389/fonc.2018.00438	Index test not relevant
Cui 2016	https://doi.org/10.1080/03007995.2016.1198312	Reference standard not relevant
Day 2019	https://doi.org/10.1177/2051415818773965	Index test not relevant
Fang 2017	http://dx.doi.org/10.1016/j.gie.2017.07.026	Excluded study design
Galetti 2019	https://doi.org/10.1177/0391560319834463	Excluded study design
Galosi 2021	https://doi.org/10.4081/aiua.2021.1.92	Excluded study design
Goldberg 2018	https://doi.org/10.1016/j.juro.2018.05.017	Index test not relevant
Gronberg 2015	http://dx.doi.org/10.1016/S1470-2045(15)00361-7	Index test not relevant
Halpern 2017	http://dx.doi.org/10.1016/j.juro.2016.08.092	Index test not relevant
Halpern 2018	https://doi.org/10.1016/j.juro.2017.10.021	Excluded study design
Irekpota 2023	https://doi.org/10.1186/s12301-019-0013-2	No population of interest
Janbaziroudsari 2016	http://dx.doi.org/10.1016/j.bulcan.2016.05.006	Index test not relevant
Jhala 2022	https://doi.org/10.5455/njppp.2022.12.02058202201032022	No population of interest
Jia 2017	https://doi.org/10.1186/s12957-017-1238-9	Indication for biopsy not relevant
Kash 2014	http://dx.doi.org/10.7314/APJCP.2014.15.7.3087	No population of interest
Kirby 2024	https://doi.org/10.3399/bjgp24X736677	Excluded publication type
Kowlessur 2020	https://doi.org/10.1007/s00345-019-02947-9	Index test not relevant
Krilaviciute 2023	https://doi.org/10.1016/j.euo.2023.09.008	Index test not relevant
Lass 2019	PMCID: PMC6853337	Excluded study design
Leal 2018	https://doi.org/10.1016/j.canep.2017.12.002	Excluded study design
Lee 2017	https://doi.org/10.1111/ajco.12596	Excluded study design
Martelin 2024	https://doi.org/10.1002/pros.24703	Excluded study design

Matsukawa 2024	https://doi.org/10.1016/j.euo.2023.12.005	No outcome of interest
Milutinovic 2023	https://doi.org/https://doi.org/10.2478/sjecr-2023-0011	No outcome of interest
Morote 2022	https://doi.org/10.3390/cancers14205100	Excluded study design
Moul 2017	http://dx.doi.org/10.1016/j.juro.2016.11.031	Excluded study design
Nepal 2023	https://doi.org/10.1016/j.ajur.2022.02.007	Index test not relevant
Pashtan 2014	http://dx.doi.org/10.1016/j.canep.2014.07.007	Index test not relevant
Prcic 2016	https://doi.org/10.5455/aim.2016.24.156-161	Index test not relevant
Roobol 2015	https://doi.org/10.1136/ebmed-2014-110162	Excluded study design
Sajjad 2022	https://doi.org/10.1177/20514158221091402	Index test not relevant
Sarkar 2022	https://doi.org/10.4103/jcrt.JCRT_1818_20	No outcome of interest
Scott 2017	https://doi.org/10.1016/j.urolonc.2016.03.013	Excluded study design
Shanbhag 2022	https://dx.doi.org/10.13005/bpj/2527	No outcome of interest
Sharma 2022	https://doi.org/10.4103/jpbs.jpbs_893_21	No population of interest
Shish 2024	https://doi.org/10.1007/s11934-024-01218-4	Excluded publication type
Shoag 2015	https://doi.org/:10.1001/jamaoncol.2015.2993.	Excluded study design
Shoag 2016	https://doi.org/10.1016/j.eururo.2016.01.009	Excluded study design
Soronen 2021	https://doi.org/10.1080/21681805.2021.1966095	Reference standard not relevant
Teoh 2015	https://doi.org/10.4103/1008-682X.144945	Relevant data not reported
Totaro 2019	https://doi.org/10.1177/0391560319834462	Excluded study design
Walden 2022	https://doi.org/10.1016/j.euros.2022.01.010	Index test not relevant
Wetterauer 2024	https://doi.org/10.1016/j.euf.2024.02.006	Index test not relevant
Yilmaz 2016	https://doi.org/10.1590/S1677-5538.IBJU.2014.0598	No outcome of interest

3.5 Clinical question 5 – PSA testing non-higher risk males

Clinical Question: *For males with no history or symptoms of prostate cancer, who are not at higher risk of clinically significant prostate cancer or prostate cancer mortality:*

- *At what age should PSA testing commence?*
- *How often should PSA testing occur?*
- *When should PSA testing cease?*
- *What PSA level should be used as a threshold to take further action/investigation?*

Systematic review report: Randomised controlled trials of PSA testing strategies for men at average or low risk of clinically significant prostate cancer or prostate cancer mortality

Authors

Suzanne Hughes, Denise Campbell, Chelsea Carle, Susan Yuill, Harriet Hui

Introduction

This review is an update of the previous systematic review undertaken for the 2016 guidelines. The previous systematic review included randomised controlled trials, pseudorandomised trials and trials in which less than 6 core systematic biopsies were used. For this update the selection criteria were narrowed to exclude pseudo-randomised trials and trials that used less than 6-core biopsies, and broadened to include the outcome metastases at diagnosis or on follow-up.

PICO

This systematic review addresses the following PICO which is summarised in detail in Table 1.

For individuals without a prostate cancer diagnosis or symptoms that might indicate prostate cancer who are not at higher risk of either clinically significant prostate cancer or of prostate cancer mortality, what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality, or the incidence of metastases at diagnosis or on follow-up?

Table 1. *PICO components*

Population	***Intervention***	***Comparator***	***Outcomes****	***Study design***
Individuals without a prior history of prostate cancer or symptoms that might indicate prostate cancer at average or low risk of clinically significant prostate cancer or prostate cancer mortality	A PSA testing strategy with or without digital rectal examination (DRE)	No PSA testing or another testing strategy	Prostate cancer-specific mortality Metastatic disease at diagnosis or on follow-up after diagnosis	Randomised controlled trials or systematic reviews thereof

** The original PICO included overall mortality as an important rather than critical outcome if resources allowed. Unfortunately there were insufficient resources to include this important but not critical outcome*

1. Methods

1.1 Revised selection criteria

Table 2. *Selection criteria*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	Modelling
Study design	Randomised controlled trials or systematic reviews thereof	Pseudo-randomised controlled trials Cohort studies
Population	Individuals with a prostate Without a prior history of prostate cancer or symptoms that might indicate prostate cancer at average or low risk of clinically significant prostate cancer or prostate cancer mortality E.g. recruited from a population registry or general population	Report symptomatic. Do not report if symptomatic and restricted to individuals attending tertiary institutions Restricted to higher risk populations e.g. people with a family history of prostate cancer or other BRCA driven cancers (breast and ovarian), germline mutation or African ancestry
Intervention	PSA testing strategy with: • or without digital rectal examination (DRE) • multiple or single/one-off screens • minimum of sextant biopsy	Quadrant biopsy used
Comparator	No PSA testing/opportunistic PSA testing Another testing strategy	
Outcome*	Prostate cancer mortality Metastatic disease at diagnosis or on follow-up after diagnosis • overall • by age groups	Metastatic disease with follow-up < 4 years** Mortality outcomes with follow-up < 14 years^ No effect estimate reported Only effect estimates reported based only on crude risks
Publication date	From 2014 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

** The original PICO included overall mortality as an important rather than critical outcome if resources allowed. Unfortunately there were insufficient resources to include this important but not critical outcome.*

*** The aim of testing or screening is to detect prostate cancer before it becomes metastatic. Any benefits of screening on the incidence of metastatic disease will not be seen immediately after the baseline screen as the initial screen will detect prevalent metastatic disease. Any benefit i.e. reduction in metastases at diagnosis or overall, will only become apparent after several years of follow-up. In the ERSPC trial a benefit started to be seen 4-5 years after randomisation (Schroder 2012).*

^ The systematic review for the 2016 guidelines found that reductions in prostate cancer specific mortality with some PSA testing protocols are apparent at 11 years follow-up if not earlier and increase with increasing follow-up (Schroder 2012). To enable and facilitate comparisons of different PSA testing protocols the length of follow up needs to be similar and long enough for any effects to become evident. A requirement of at least 14 years median follow-up was chosen as the three most recent trials comparing PSA testing with usual care report prostate cancer mortality at 14-16 years median follow-up.

1.2 Definitions and terminologies

For the purpose of this review:

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7 (3+4) or higher on histopathological findings (Epstein 2016).

Metastatic disease refers to M1 disease or a PSA level > 100 ng/mL if imaging not available.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- *Urological Society of Australia and New Zealand (USANZ) website*

- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest and meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence, demonstrate a transparent link between the systematic review of the evidence and the recommendations, and, as the evidence for PSA testing for prostate cancer continues to evolve, be based on literature published up until 2023 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

For the 2016 guidelines systematic review, systematic reviews included in a NHMRC evaluation of the evidence for prostate cancer screening in 2013 (NHMRC 2013a) were used to identify relevant articles published up until 2012. Medline, Embase, CENTRAL, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched to identify relevant articles published from 2012 until 1st March 2014. Medline, Embase and CENTRAL databases were searched from 2012 onwards for relevant articles using search terms for prostate cancer and PSA screening coupled with filters for randomised controlled trials. To identify studies that considered Aboriginal and Torres Strait Islander peoples these searches were then combined with search terms for Aboriginal and Torres Strait Islander peoples. A complete list of the terms used for all search strategies are included as Appendix A.1. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles. The full texts identified by these searches for further evaluation were reassessed for inclusion in the current systematic review update.

To find evidence published from 2014 onwards the Cochrane Database of Systematic Reviews was searched on 13th March 2024 using the term “prostate” and scoping searches were undertaken to identify recent systematic reviews of randomised controlled trials comparing PSA testing with usual care. Two systematic reviews (Ilic 2018, Paschen 2022) were identified that were considered to cover the relevant literature up to 2019 and consequently, could be used to identify potentially relevant articles up to 2019. To identify potentially relevant articles published from 2019 onwards Medline and Embase databases were searched on the 18th March 2024 by combining text words and subject headings for prostate cancer, PSA and screening, together with a filter for randomised controlled trials (RCT/CCT - MEDLINE, Embase search filter. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 2023-11-30). The Cochrane Central Register of Controlled Trials was searched on the 20th March 2024 using a similar search strategy without the filter for randomised controlled trials. These searches were limited to articles published in English from 1st January 2019 onwards, with monthly alerts capturing articles published until the final

literature cut-off date, 1st September 2024. The searches were designed to identify potentially relevant trials in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the searches are included in Appendix A.2. Titles and abstracts were screened by one reviewer. Full texts of potentially relevant articles were retrieved and were assessed independently by two reviewers. Differences were resolved by discussion. Reference lists of recent relevant guidelines and full texts retrieved for further assessment were checked for potential additional articles.

1.5 Data extraction and analyses

Data was extracted from studies identified from the original 2016 systematic review and the 2024 search update that met the revised selection criteria. One reviewer extracted data from the included studies which was then checked by a second reviewer. The following study characteristics were extracted; country and year of publication, participant number, eligibility and age, setting and enrolment period, intervention components, description or components of comparator arm, relevant outcomes reported, median follow-up and time frame, subgroup data available, and additional information regarding notable study limitations and possible sources of bias. Effect estimates based on person-years at risk and their 95% confidence intervals and risks in the control arm were extracted as reported in the study. Any differences were resolved by discussion or by a third reviewer.

For the summary of findings table, where effect estimates for a given protocol were reported at difference lengths of follow-up, preference was given to follow-up of 14-16 years follow-up in order to optimise comparisons of the effects of different protocols on prostate cancer mortality. Where different metrics of the control risk were reported, preference was given to cumulative risk over crude risk.

The risks in the intervention arm and the absolute difference between the control and intervention arms were estimated following GRADE guidance outlined in the GRADE Handbook (Schunemann 2013). The magnitude of the absolute difference was determined using thresholds for small, moderate and large absolute effects. These thresholds were determined by a reference group consisting of a consumer, general practitioner and clinical specialist working group members.

Pooled analyses were planned where there were two or more studies reporting the same outcome at corresponding time points.

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias for each of the critical outcomes reported by the included individually randomised controlled trials using the Cochrane Collaboration Risk of Bias-II tool (Sterne 2019) and included cluster-randomised controlled trials using an adaptation of the Cochrane risk-of-bias tool for randomised trials (RoB 2.0) for cluster-randomized trials (Eldridge 2021).

Disagreements in ratings were resolved by discussion or by a third reviewer. The risk of bias for each outcome for each study was rated low, some concerns or high for the following sources of bias; the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result, and for cluster randomised controlled trials, timing of identification or recruitment of participants.

1.7 GRADE assessment of certainty of evidence

GRADE assessments of the certainty of the body of evidence were undertaken for each critical outcome (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence). For this systematic review prostate cancer mortality and metastases on diagnosis or progression were considered critical outcomes.

The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias of the body of evidence based on guidance from the GRADE Handbook (Schunemann 2013) and on guidance for assessing narrative syntheses provided by Murad 2017. For the assessment of risk of bias, contamination i.e. PSA testing in the absence of symptoms, in the control group was considered the most important potential source of bias likely distorting effect estimates towards the null. Imprecision was assessed in the context of whether there was a clinically important decrease rather than the magnitude of the decrease, using thresholds for a minimal clinically important difference (MCID) or small absolute difference. These thresholds were determined by a reference group consisting of a consumer, a general practitioner, a urology nurse practitioner and clinical specialists following GRADE guidance provided by Schunemann 2022. Potential publication bias (or small study effects) was assessed using a Funnel Plot if 10 or more studies. Where there were less than 10 studies, clinical trial registries were searched for potentially relevant trials (see Section 1.8 below for search details) that had planned completion dates prior to 2020 (5 or more years ago), that had not been terminated and for which results had not been published suggesting publication bias.
As per GRADE guidance, randomised controlled trials started with a high level of certainty in the evidence and were downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.
Definitions of the GRADE ratings of certainty of the overall body of evidence for each outcome are presented in Appendix B.

1.8 Clinical trial registry searches

Potentially relevant ongoing and unpublished trials were identified from literature searches, recent guidelines and by clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 20th March 2025.

The clinical trial registries were searched with the search terms listed below:
Clinicaltrials.gov using the terms:
“prostate cancer” and “screening”
“prostate cancer” and “detection/screening”
“prostate cancer” and “test”
“prostate cancer” and “PSA”

International Clinical Trials Registry Platform using the terms:
“prostate cancer” and “screening”

"prostate cancer" and "detection"
"prostate cancer" and "test"
"prostate cancer" and "PSA"

Australia and New Zealand Clinical Trial Registry using the terms:
"prostate cancer" and "early detection/screening" or "diagnosis/prognosis"
"prostate cancer" and "screening"
"prostate cancer" and "detection"
"prostate cancer" and "test"
"prostate cancer" and "PSA"

2. Results

2.1 Guideline searches

Two potentially relevant guidelines were identified which were reportedly based on systematic reviews of literature published up until 2023 or later. They were not considered for adoption; for both guidelines the systematic reviews of the evidence were not accessible, and for one of the guidelines risk of bias and GRADE assessments were not mentioned in the reported systematic review methods. (Appendix C).

2.2 Literature searches

A total of 12 articles reporting on 3 randomised controlled trials were included in this systematic review. Figure 1 outlines the process for identifying relevant articles published from 1990 onwards. An appraisal of the 33 full texts considered for the 2016 guidelines identified two articles for inclusion. For the literature searches for the 2025 guidelines update, eighteen potentially relevant articles were identified from the Ilic 2018 and Paschen 2022 systematic reviews. The Medline, Embase and CENTRAL database searches retrieved 158 unique citations which were assessed by one reviewer of which 52 articles were retrieved for a more detailed evaluation by two reviewers. Five articles were identified for full text evaluation from scoping searches or from reference lists of recent relevant guidelines and full texts retrieved for further assessment. Of the 75 articles evaluated for inclusion ten met the inclusion criteria. There were no studies that included Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.
The retrieved articles that were not included in this review and the reasons for their exclusion are documented in Appendices D and E. The main reasons for exclusion were no relevant outcomes and excluded study design.

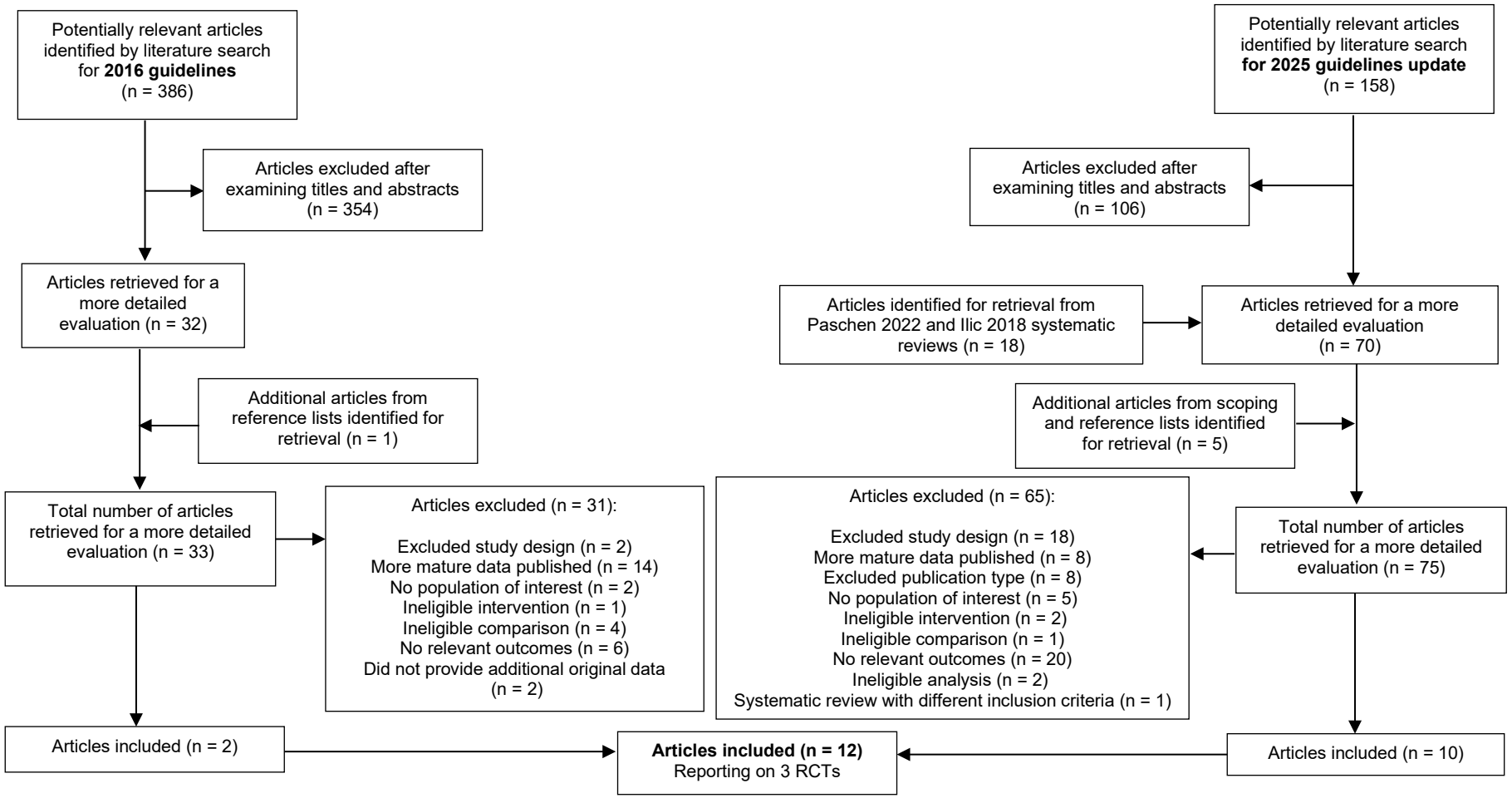

Figure 1. *Process of inclusion and exclusion of published articles*

2.3 Characteristics of included studies

Characteristics of included studies are described in Table 3.

Table 3. *Characteristics of randomised controlled trials comparing PSA testing strategies ± DRE compared to no PSA testing reporting outcomes of prostate cancer-specific mortality, and/or incidence of metastases at diagnosis or on follow-up for individuals at average risk of prostate cancer*

Study	*Setting and enrolment period*	*Participants*	*Intervention*	*Comparison*	*Relevant Outcomes*	*Comments*
Pinsky 2019 (Cancer) **Pinsky 2019** (BJU Int) (USA) *Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)* *NCT00002540*	10 tertiary institutions 1993-2001	Men aged 55-74 years Exclusions: Included personal history of prostate, lung or colorectal cancer, used finasteride in last 6 months or currently receiving cancer treatment From April 1995, men reporting more than one PSA test in the previous 3 years also excluded **N = 76,683** Median age: 63 years 88% Non-Hispanic white ~ 50% had received PSA test in 3 years prior to enrolment	Annual PSA testing for 6 years PSA threshold > 4.0ng/mL Plus Annual DRE for the first 4 years **N = 38,340** 84% (average) underwent testing each year 32% and 22% underwent biopsy following positive PSA test and DRE respectively in screening arm	Usual care (included opportunistic screening) **N = 38,343** 46% had a PSA test in previous year as part of routine health check-up	**Prostate cancer-specific mortality** Median follow-up: 16.7-16.9 years **Metastases at diagnosis** Median follow-up: 15.1-15.3 years **Metastases at diagnosis or on progression** Median follow-up: 12.8-12.9 years	% PSA testing in control arm derived from annual questionnaires All participants provided written informed consent Until 2011 diagnosed cancers, deaths, and causes of death were ascertained by annual follow-up questionnaire and periodic linkage to the National Death Index. From 2011 onwards outcomes determined by linkages to state cancer registries to assess cancer incidence and linkages to the National Death Index to assess mortality. Cause of death determined by a blinded endpoint verification process that utilized relevant medical records. Of those alive at the time of the transition, 11.2% of intervention arm versus 15.2% of usual care arm men refused further follow-up.
Martin 2024 (UK) *Cluster Randomized Trial of PSA testing for Prostate Cancer (CAP)*	573 participating primary care practices in England and Wales 2002-2009	Men aged 50-69 years routinely attending a participating primary care practice Exclusions: Prostate cancer or death pre-randomisation, no or untraceable NHS digital record, registered with participating	Single invitation to undergo single PSA test PSA threshold ≥ 3.0 ng/mL Biopsy: Transrectal 10-core	Usual care No formal invitation to undergo PSA test - followed according to standard medical practice (current UK policy was not to recommend screening)	**Prostate cancer-specific mortality** Median follow-up: 15.4 years	Randomisation preceded inviting practices to take part in the study. 573/911 practices randomised eligible and participated in study Prostate cancer-specific mortality defined as a death where prostate cancer was

ISRCTN92187251		practice on temporary or emergency basis **N = 415,357** Mean age: 59.0 years Race/ethnicity: NA % previous PSA test NR	271 participating primary care practices **N = 195,912** 96.6% analysed Race/ethnicity: 98% white 40% had PSA test 85% of those with PSA between 3.0-19.9 ng/mL underwent biopsy as per protocol	302 participating primary care practices **N = 219,445** > 99.9% analysed Race/ethnicity: NA Indirectly estimated cumulative PSA testing at 10-15% over a median of 10 years of follow-up		considered the definite or probable cause of death or a prostate cancer treatment-related-death by independent cause of death committee All-cause mortality data was obtained by linkage to the Office for National Statistics Intention to treat analyses Using data from other GP practices Clift 2021 estimated 10-year PSA testing rate 23% (symptomatic and asymptomatic) for similar period Individual informed consent sought from men in intervention arm who attended PSA testing but not from men in control arm
Hugosson 2019 **Buzzoni 2015** **Schroder 2012** (Belgium, Finland, Italy, The Netherlands, Spain, Sweden, Switzerland) *The European Randomised Study of Screening for Prostate Cancer (ERSPC)* *ISRCTN49127736*	Male populations in regions of 7 European countries 1991-2003	Men aged 50-74 years identified in population registers Exclusions: Personal history of prostate cancer, diagnosed with prostate cancer, died or emigrated between randomisation and screening invitation French data not included by authors as < 50% screening participation N = 182,160 ***Core age group*:** **Age 55 – 69 years at baseline** **N = 162,241** Median age: 60 years Race/ethnicity: NR % previous PSA test NR	Invited to screening for prostate cancer Different screening protocols in different countries Most countries offered screening starting at ages 55-74 years at 4-year intervals until age 75 and used PSA as the primary test with thresholds of 3.0-4.0 ng/mL Biopsy recommended for all men with positive test Biopsy: Initially sextant biopsy recommended Later 10-12 core biopsy recommended **N = 72,890**	Usual care (included opportunistic screening) No invitation to screen for prostate cancer **N = 89,351**	**Prostate cancer-specific mortality** Median follow-up: 16 years (truncated at 16 years) **Metastases at diagnosis** Truncated at 13-year follow-up	Randomisation performed at each centre During 1994 and 1995, performance criteria were established which included randomisation with concealed allocation. A uniform PSA method was chosen (Tandem R; Hybritech) and a quality assurance programme was designed to guarantee accuracy of the test across centres Results were obtained by linkage to local cancer registries for prostate cancer incidence and national registries for overall mortality If consent obtained after randomisation (Sweden,

		Subgroup analysis by age at baseline *Results provided for each country* – all except Switzerland had a median follow-up ≥ 15 years	83% screened at least once 85.6% of screen-positive tests followed by a biopsy Number of screening invitations: 2-8 Duration of screening: 4-16 years	Contamination estimates varied or not reported for individual centres		Finland and Italy) 75% of those in screening arm underwent at least one PSA test If consent obtained before randomisation 90% of those in screening arm underwent at least one PSA test Determination of prostate cancer as a cause of death blinded Blinding as to ascertainment of stage at diagnosis: NR Intention to treat analyses Staging data derived from/ assigned by population-based cancer registries with additional information on staging and treatment were recovered "from medical records in a non-differential way for all cases in both arms" Stage data missing for 8% and 10% of cancers in screening and control arm respectively Imputed missing data
		Subgroup with results for metastases on diagnosis or follow-up: 4 countries: Finland (Tampere), The Netherlands, Sweden Switzerland **N = 76,813**	**N = 36,270** % screened at least once: NR % of screen-positive tests followed by a biopsy: NR	**N = 40,543** Contamination: NR	**Metastases at diagnosis or on progression** Median follow-up: 12.0 years	Some ERSPC centres did not have relevant data for this outcome Blinding as to ascertainment of outcome: NR Follow-up of cancer cases in the control arm was by 6-month chart review Diagnostic and treatment decisions determined by regional care providers

Hugosson 2019	***ERSPC Belgium*** Antwerp 1991-2003	Men aged 55-74 years identified in population registers ***Core age group*:** **Age 55 – 69 years at baseline** **N = 8562** Median age: 63 years % previous PSA test NR	Invited to screening for prostate cancer Age at start of screening **55-74** years Screening interval: **4 years** (first interval between screens up to 7 years) Screening discontinued after age 74 or 3 screens Screening tests *1992 – 1994* PSA + DRE + TRUS PSA cut-off **≥ 10ng/mL** *1995 – 1997* PSA + DRE + TRUS PSA cut-off **≥ 4 ng/mL** *1998* **PSA** only PSA cut-off **≥ 4 ng/mL** *1999 onwards* PSA cut-off **≥ 3 ng/mL** Biopsy: Initially sextant biopsy recommended **N = 4307** 91% screened at least once 71% of screen-positive tests followed by a biopsy Screens per man (mean): 1.5 Number of screening invitations: NR Duration of screening: NR	Usual care (included opportunistic screening) No invitation to screen for prostate cancer Referred to own GP for routine check-up which could include DRE as this was considered general practice for older men in Belgium **N = 4255** Contamination estimates NR	**Prostate cancer-specific mortality** Median follow-up: 16 years (truncated at 16 years)	Consent obtained before randomisation i.e. all men consented Men diagnosed with prostate cancer decided with GP on treatment
Hugosson 2019	***ERSPC Finland*** Helsinki and Tampere 1996-1999	Men aged 55, 59, 63 and 67 years identified in population registers	Invited to screening for prostate cancer Age at start of screening **55, 59, 63 and 67** years Screening interval: **4 years** Screening discontinued after age 71 or 3 screens	Usual care (included opportunistic screening) No invitation to screen for prostate cancer Not contacted	**Prostate cancer-specific mortality** Median follow-up: 16 years (truncated at 16 years)	The randomisation was undertaken at the Population Registry using computer-generated pseudorandom numbers. Consent obtained after randomisation – only those in screening arm consented

		***Core age group*:** **Age 55 – 69 years at baseline** **N = 80,379** Median age: 59 years Previous PSA test: 0.7%	Screening tests PSA cut-off **≥ 4.0 ng/mL** PSA 3.0 – 3.9 ng/mL: triage to biopsy using DRE until 1998 and from 1999 using free-to-total PSA Biopsy: Sextant biopsy with directed biopsy for focal lesions replaced in 2002 by 10–12 core biopsies **N = 31,970** 74% screened at least once 91% of screen-positive tests followed by a biopsy Screens per man (mean): 1.6 Number of screening invitations: 2-3 Duration of screening: 4-8 years	**N = 48,409** 7.8% received PSA test 1996-1999 62.7% had received PSA test at 12 years follow-up However, no data on PSA testing of asymptomatic men		Information on cancer deaths obtained from Statistics Finland
Hugosson 2019	***ERSPC Italy*** Florence 1996-2000	Men aged 55-74 years identified in population registers ***Core age group*:** **Age 55 – 69 years at baseline** **N = 14,515** Median age: 62 years % previous PSA test NR	Invited to screening for prostate cancer Age at start of screening **55-74** years Screening interval: **4 years** Screening discontinued after age 74 Screening tests PSA cut-off **≥ 4.0 ng/mL** PSA 2.5 – 3.9 ng/mL: triage to biopsy using DRE and TRUS Biopsy: Sextant biopsy with directed biopsy for focal lesions **N = 7265** 79% screened at least once	Usual care (included opportunistic screening) No invitation to screen for prostate cancer **N = 7250**	**Prostate cancer-specific mortality** Median follow-up: 15 years (truncated at 16 years)	Consent obtained after randomisation

			63% of screen-positive tests followed by a biopsy Screens per man (mean): 1.8 Number of screening invitations: 2-6 Duration of screening: > 4- to < 16 years	~30% reported had received PSA test in last year However, no data on PSA testing of asymptomatic men		
Hugosson 2019 **De Vos 2023**	***ERSPC Netherlands*** Rotterdam 1993-2000	Men aged 55-74 years identified in population registers **N = 41,900** Median age: 63 years Previous PSA test: ~13%	Invited to screening for prostate cancer Age at start of screening **55-74** years Screening interval: **4 years** Screening discontinued after age 74 Screening tests *1993 – 1995* PSA + DRE + TRUS PSA cut-off **≥ 4ng/mL** *1995 – 1997* PSA only PSA cut-off **≥ 4ng/mL** If PSA 1.0 – 3.9ng/mL DRE + TRUS *1997 onwards* PSA cut-off **≥ 3ng/mL** Biopsy: Sextant biopsy **N = 20,984** 95% screened at least once 91% of screen-positive tests followed by a biopsy Screens per man (mean): 2.3	Usual care (included opportunistic screening) No invitation to screen for prostate cancer **N = 20,916** Contamination not assessed	**Prostate cancer-specific mortality** Median follow-up: 21 years **Metastases at diagnosis or on progression** Median follow-up: NR	Consent obtained before randomisation i.e. all men consented
		***Core age group*:** **Age 55 – 69 years at baseline** **N = 34,833** Median age = 62 years Previous PSA test: ~13%	**N = 17,443** 95% screened at least once 89% of screen-positive tests followed by a biopsy Screens per man (mean): 2.3 Number of screening invitations: 2-5	**N = 17,390** Estimated 19.4% had received screening PSA test at 13 years follow-up – 50% of all PSA tests (Bokhorst 2014)	**Prostate cancer-specific mortality** Median follow-up: 16 years (truncated at 16 years) Median follow-up: 21 years (truncated at 21 years)	

			Duration of screening: 4?- to 16 years		**Metastases at diagnosis** Median follow-up: NR **Metastases at diagnosis or on progression** Median follow-up: NR	
Hugosson 2019 **Lujan Galan 2020**	***ERSPC Spain*** Madrid 1996-1999	Men aged 45-70 years identified in population registers **N = 4276** Median age: 57 years % previous PSA test NR	Invited to screening for prostate cancer Age at start of screening 45-70 years Screening interval: **4 years** Screening discontinued after age 74 or 3 screens Screening tests PSA cut-off **≥ 3.0 ng/mL** Biopsy: Sextant biopsy with directed biopsy for focal lesions **N = 2415**	Usual care (included opportunistic screening) No invitation to screen for prostate cancer **N = 1861**	**Prostate cancer-specific mortality** Median follow-up: 21.1 years	Consent obtained before randomisation i.e. all men consented
		***Core age group*:** **Age 55 – 69 years at baseline** **N = 2197** Median age: 60 years % previous PSA test NR	**N = 1056** 100% screened at least once 74% of screen-positive tests followed by a biopsy Screens per man (mean): 1.7 Number of screening invitations: 2-6 Duration of screening: > 4- to < 16 years	**N = 1141** Contamination not assessed	**Prostate cancer-specific mortality** Median follow-up: 16 years (truncated at 16 years)	
Hugosson 2019 **Hugosson 2018** **Franlund 2022** **Hugosson 2010** *ISRCTN54449243*	***ERSPC Sweden*** Goteborg December 1994	Men aged 50-64 years identified in population registers	Invited to screening for prostate cancer Age at start of screening 50-64 years Screening interval: **2 years** Screening discontinued after age 69	Usual care (included opportunistic screening) No invitation to screen for prostate cancer	**Prostate cancer-specific mortality** Median follow-up: 18 years (truncated at 18 years)	Consent obtained after randomisation No informed consent sought from those allocated to usual care Participants allocated to usual care not informed about being included in a prostate cancer

		N = 19,894 Median age: 56 years Previous PSA test: 4.2-4.6%	Screening tests <u>*1995 – 1998*</u> PSA cut-off **≥ 3.4 ng/mL** <u>*1999 – 2004*</u> PSA cut-off **≥ 2.9 ng/mL** <u>*2005 onwards*</u> PSA cut-off **≥ 2.5 ng/mL** Biopsy: Sextant biopsy replaced in 2009 with 10-core biopsy **N = 9945** 77% screened at least once Number of screening invitations: 3-10 Maximum duration of screening: 20 years	**N = 9949** 72% men in control group had at least 1 PSA test during follow-up No data on PSA testing of asymptomatic men	Median follow-up: 22 years (truncated at 22 years)	screening trial only that they belonged to a control group in a cancer study Treatment per risk group was similar between the arms
		***Core age group*:** **Age 55 – 64 years at baseline** **N = 11,852** Median age: 60 years % Previous PSA test: NR	**N = 5901** 76% screened at least once 87% of screen-positive tests followed by a biopsy Screens per man (mean): 2.6 Number of screening invitations: 3- 8 Maximum duration of screening: 16 years	**N = 5951** No data on PSA testing of asymptomatic men	**Prostate cancer-specific mortality** Median follow-up: 16 years (truncated at 16 years)	

DRE = digital rectal examination; N = number; NA = not available; NR = not reported; PSA = prostate-specific antigen; TRUS = transrectal ultrasound

2.4 Results by outcomes of interest

Prostate cancer mortality: Three randomised controlled trial identified – Results reported in Table 4

Metastatic disease: Two randomised controlled trials identified – Results reported in Table 5

Table 4. *Results of randomised controlled trials comparing PSA testing strategies ± DRE compared to no PSA testing for the outcome of prostate cancer-specific mortality for individuals at average risk of prostate cancer*

Study	N	PSA testing protocol				Median follow up	Time frame	Risk in control arm per 10000	Effect estimate and 95%CI	Estimated risk in intervention arm (95%CI) per 10000	Absolute difference (95% CI) per 10000	Number needed to invite
		Age at start of screening	PSA threshold	Screening interval	Screening duration							
PLCO – PSA + DRE testing												
Pinsky 2019 BJUI	76,683	55-74 years	4 ng/mL	1 year	6 years	16.7-16.9 years	21 years	91.8 (352/38343)^	RR = 0.93 (0.81 – 1.08)	85.4 (74.4-99.1)	6 fewer (17 fewer to 7 more)	1667
Pinsky 2019 BJUI	76,683	55-74 years	4 ng/mL	1 year	6 years	16.7-16.9 years	16 years	~62.3 (239/38343)^	RR = 0.93 (0.81 – 1.08)	57.9 (50.5-67.3)	4 fewer (12 fewer to 5 more)	2500
CAP – single PSA test												
Martin 2024	415,357	50-69 years	3 ng/mL	Single screen	0 years	15.4 years	15 years	78*^	RR* = 0.92 (0.85-0.99)	72 (66 – 77)	6 fewer (12 fewer to 1 fewer)	1667
	Sub-analyses by age											
	NR	50-54 years	3 ng/mL	Single screen	0 years	NR	15 years	25*^	RR** = 0.96 (0.76-1.22)	24 (19-31)	1 fewer (6 fewer to 6 more)	10,000
	NR	55-59 years	3 ng/mL	Single screen	0 years	NR	15 years	54*^	RR** = 0.92 (0.78-1.10)	50 (42-59)	4 fewer (12 fewer to 5 more)	2500
	NR	60-64 years	3 ng/mL	Single screen	0 years	NR	15 years	110*^	RR** = 0.90 (0.77-1.04)	99 (85-114)	11 fewer (25 fewer to 4 more)	909
	NR	65-69 years	3 ng/mL	Single screen	0 years	NR	15 years	176*^	RR** = 0.98 (0.86-1.12)	172 (151-197)	4 fewer (25 fewer to 21 more)	2500
ERSPC – primarily PSA test only												
Hugosson 2019	162,241	55-69 years	Primarily 3-4 ng/mL	Primarily 4 years	Primarily until age 74 years	16 years	16^^ years	89.2**^	RR = 0.80 (0.72-0.89)	71.4 (64.2-79.4)	18 fewer (25 fewer to 10 fewer)	556
	Sub-analyses by age											
	NR	55-59 years	Primarily 3-4 ng/mL	Primarily 4 years	Primarily until age 74 years	NR	16^^ years	NR	RR = 0.76 (0.62-0.92)	Not calculable	Not calculable	NR
	NR	60-64 years	Primarily 3-4 ng/mL	Primarily 4 years	Primarily until age 74 years	NR	16^^ years	NR	RR = 0.93 (0.76-1.12)	Not calculable	Not calculable	NR

	NR	64-69 years	Primarily 3-4 ng/mL	Primarily 4 years	Primarily until age 74 years	NR	16^^ years	NR	RR = 0.74 (0.62-0.90)	Not calculable	Not calculable	NR
ERSPC Belgium PSA test +/- DRE and TRUS												
Hugosson 2019	8562	55-69 years	3-10 ng/mL	4-7 years	Until age 74 years or after 3 screens	16 years	16^^ years	89.2*^*	RR = 0.78 (0.44-1.34)	69.6 (39.2-119.5)	20 fewer (50 fewer to 30 more)	500
ERSPC Finland PSA test only												
Hugosson 2019	80,379	55, 59, 63 and 67 years	4 ng/mL Triage tests if 3.0-3.9 ng/mL	4 years	Until age 71 years or after 3 screens	16 years	16^^ years	89.2*^*	RR = 0.91 (0.77-1.06)	81.2 (68.7-94.6)	8 fewer (21 fewer to 5 more)	1250
ERSPC Italy PSA test only												
Hugosson 2019	14,515	55-69 years	4 ng/mL Triage tests if 2.5-3.9 ng/mL	4 years	Until age 74 years	15 years	16^^ years	89.2*^*	RR = 0.99 (0.66-1.49)	88.3 (58.9-132.9)	1 fewer (30 fewer to 44 more)	10,000
ERSPC The Netherlands PSA test +/- DRE and TRUS												
Hugosson 2019	34,833	55-69 years	3-4 ng/mL	4 years	Until age 74 years	16 years	16^^ years	89.2*^*	RR = 0.67 (0.53-0.85)	59.8 (47.3-75.8)	29 fewer (42 fewer to 13 fewer)	345
De Vos 2023	34,833	55-69 years	3-4 ng/mL	4 years	Until age 74 years	21 years	21^* years	159	RR = 0.73 (0.61-0.88)	116.1 (97.0-139.9)	43 fewer (62 fewer to 19 fewer)	233
	41,900	55-74 years	3-4 ng/mL	4 years	Until age 74 years	21 years	21^* years	NR	RR = 0.83 (0.71-0.97)	Not calculable	Not calculable	355
ERSPC Spain PSA test only												
Hugosson 2019	2197	55-69 years	3 ng/mL	4 years	Until age 74 years or after 3 screens	16 years	16^^ years	89.2*^*	RR = 0.65 (0.13-2.63)	58.0 (11.6-234.6)	31 fewer (78 fewer to 145 more)	323
Lujan Galan 2020	4276	45-70	3 ng/mL	4 years	Until age 74 years or after 3 screens	21 years	21 years	40	NR	Not calculable	Not calculable	
ERSPC Sweden PSA test only												
Hugosson 2019	11,852	55-64 years	2.5-3.4 ng/mL	2 years	Until age 69 years	16 years	16^^ years	89.2*^*	RR = 0.63 (0.44-0.88)	56.2 (39.2-78.5)	33 fewer (50 fewer to 11 fewer)	303
Hugosson 2010	19,904	50-64 years	2.5-3.4 ng/mL	2 years	Until age 69 years	14 years	14 ^*^ years	90*^	RR = 0.56 (0.39-0.82)	50.4 (35.1-73.8)	40 fewer (55 fewer to 16 fewer)	250
Hugosson 2018	19,899	50-64 years	2.5-3.4 ng/mL	2 years	Until age 69 years	18 years	18 ^^^ years	150*^	RR = 0.65 (0.49-0.87)	97.5 (73.5-130.5)	53 fewer (77 fewer to 20 fewer)	231

Franlund 2022	19,894	50-64 years	2.5-3.4 ng/mL	2 years	Until age 69 years	22 years	22^^* years	213*^	RR = 0.71 (0.55-0.91)	151.2 (117.2-193.8)	62 fewer (96 fewer to 19 fewer)	217
	19,894	50-64 years	2.5-3.4 ng/mL	2 years	Until age 69 years	22 years	22^^* years	170*^ #	RR = 0.71 (0.55-0.91)	120.7 (93.5-154.7)	49 fewer (77 fewer to 15 fewer)	204

^ Crude risk estimated by technical team using number of prostate cancer deaths estimated from Figure 1 in Pinsky 2019 BJUI
** Calculated taking into account age at analysis and clustering*
*** Calculated taking into account clustering*
^ Data truncated at 14 years follow-up*
^^ Data truncated at 16 years follow-up
^^^ Data truncated at 18 years follow-up
^^* Data truncated at 22 years follow-up
*** Risk based on Poisson distribution*
**^* Risk based on Poisson distribution for all ERSPC centres combined as control risk for individual ERSPC centres not reported*
**^ Cumulative probability of event*
 # competing risks taken into account
CAP = Cluster Randomized Trial of PSA testing for Prostate Cancer; CI = confidence interval; DRE = digital rectal examination; ERSPC = European Randomised Study of Screening for Prostate Cancer; N = number; NR = not reported; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR = rate ratio or risk ratio; PSA = prostate-specific antigen; TRUS = transrectal ultrasound

Table 5. *Results of randomised controlled trials comparing PSA testing strategies ± DRE compared to no PSA testing for the outcome of metastases at diagnosis or on progression for individuals at average risk of prostate cancer*

Study	N	PSA testing protocol				Median follow up	Time frame	Risk in control arm per 10000	Effect estimate and 95%CI	Estimated risk in intervention arm (95%CI) per 10000	Absolute difference (95% CI) per 10000
		Age at start of screening	PSA threshold	Screening interval	Screening duration						
PLCO - PSA + DRE testing											
Pinsky 2019 Cancer	76,683	55-74 years	4 ng/mL	1 year	6 years	12.8-12.9 years	15 years	80*^	RR = 0.98 (0.81-1.18)	78 (65-95)	2 fewer (15 fewer to 15 more)
	76,683	55-74 years	4 ng/mL	1 year	6 years	12.8-12.9 years	16 years	58.4^ (224/38343)	RR = 0.98 (0.81-1.18)	57.2 (47.3-68.9)	1 fewer (11 fewer to 11 more)
	76,683	55-74 years	4 ng/mL	1 year	6 years	12.8-12.9 years	12 years	~54*	RR = 0.98 (0.81-1.18)	53 (44-64)	1 fewer (10 fewer to 10 more)
ERSPC – primarily PSA test only											
Schroder 2012	76,813	55-69 years	Primarily 3-4 ng/mL	Primarily 4 years	Primarily until age 74 years	12 years	12 years	~104**	RR = 0.70 (0.60-0.82)	72.8 (62.4-85.3)	31 fewer (42 fewer to 19 fewer)
	76,813	55-69 years	Primarily 3-4 ng/mL	Primarily 4 years	Primarily until age 74 years	12 years	~16 years	101^ (410/40543)	RR = 0.70 (0.60-0.82)	70.7 (60.6-82.8)	30 fewer (40 fewer to 18 fewer)
ERSPC The Netherlands PSA test +/- DRE and TRUS											
De Vos 2023	34,833	55-69 years	3-4 ng/mL	4 years	Until age 74 years	21 years	21^* years	349^^	RR = 0.67 (0.58-0.78)	233.8 (202.4-272.2)	115 fewer (147 fewer - 77 fewer)

	41,900	55-74 years	3-4 ng/mL	4 years	Until age 74 years	21 years	21^* years	NR	RR = 0.74 (0.65-0.84)	Not calculable	Not calculable

^ Crude rate for entire follow-up
**^ Cumulative probability of event*
** Cumulative probability of event at 12 years estimated by technical team from Figure 2 in Pinsky 2019 Cancer*
*** Cumulative probability of event at 12 years estimated by technical team from Figure 2a in Schroder 2012*
^ Data truncated at 21 years follow-up*
^^ Cumulative probability of event at 21 years estimated by technical team from Figure 2A in De Vos 2023
DRE = digital rectal examination; CI = confidence interval; ERSPC = European Randomised Study of Screening for Prostate Cancer; N = number; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA = prostate-specific antigen; RR = rate ratio; TRUS = transrectal ultrasound

2.5 Risk of bias

The results of the risk of bias assessments for the included studies are shown in Tables 6 and 7.

Table 6. *Risk of bias assessments for included studies of randomised controlled trials studies using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) (Sterne 2019)*

Outcome	Study	Source of bias					Overall risk of bias
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	
Prostate cancer-specific mortality	PLCO (Pinsky 2019 BJU)	Low	High	Some concerns	Low	Low	High
	ERSPC Belgium	Some concerns	Some concerns	Low	Low	Low	Some concerns
	ERSPC Finland	Low	Low	Low	Low	Low	Low
	ERSPC Italy	Low	Low	Low	Low	Low	Low
	ERSPC Netherlands	Some concerns	Some concerns	Low	Low	Low	Some concerns
	ERSPC Spain	Low	Some concerns	Low	Low	Low	Some concerns
	ERSPC Sweden	Low	Low	Low	Low	Some concerns	Some concerns
Metastases at diagnosis or on progression	PLCO (Pinsky 2019 Cancer)	Low	High	High	High	Some concerns	High
	ERSPC Finland, The Netherlands, Sweden, Switzerland (Schroder 2012) (Schroder 2012)	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
	ERSPC The Netherlands (de Vos 2023)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns

ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

Table 7. *Risk of bias assessments for included cluster-randomised controlled trials using the Cochrane risk-of-bias tool for randomised trials (RoB 2.0) RoB 2 tool adapted for cluster-randomised trials (Eldridge 2021)*

Outcome	Study	Source of bias						Overall risk of bias
		Randomisation process	Timing of identification or recruitment of participants	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	
Prostate cancer-specific mortality	CAP (Martin 2024)	High	Low	Low	Low	Low	Low	High

CAP = Cluster Randomized Trial of PSA Testing for Prostate Cancer

Key to overall rating
Low risk of bias: "Low" for all domains
Some concerns regarding risk of bias: "Some concerns" but not "high" for one or more domains
High risk of bias: "High" for one or more domains

3. GRADE assessments of the certainty of the evidence

Prostate cancer mortality – assessments are shown in Table 8

Metastases at diagnosis or on progression – assessments are shown in Table 9

Table 8. *GRADE assessment of the certainty of the evidence for prostate cancer mortality from randomised controlled trials comparing a PSA testing protocol with usual care in an average risk population*

GRADE domain	*Rating*	*Reason for rating*	*Certainty of evidence*
Annual PSA testing using a threshold of 4 ng/mL for 6 years + annual DRE for 4 years starting at age 55-74 years			
Risk of bias	Serious concerns	For the single trial reporting on this protocol, the PLCO trial, the risk of bias due to deviations from intended interventions was considered high with 46% of those in the usual care arm receiving a PSA test as part of routine health check-up in the past year during the first 6 years of the trial likely leading to the underestimation of the effects of the intervention.	*LOW*
Indirectness	Serious concerns	Approximately 50% of participants had received a PSA test in the 3 years prior to enrolment. In addition, participants were recruited by 10 tertiary care institutions rather than the general population. Consequently, the results may not be directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	No serious concerns	Based on a rate ratio at 16 years of 0.93 with a 95% confidence interval of 0.81 to 1.08, in a population of 10,000 men annual PSA testing for 6 years using a threshold of 4 ng/ml starting at ages 55-74 years plus an annual DRE for the first 4 years is estimated to result in 4 fewer (12 fewer to 5 more) prostate cancer deaths when compared with usual care. Using a MCID of 16 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 32 prostate cancer deaths per 10,000 and 64 prostate cancer deaths per 10,000, the absolute difference between the two arms was a clinically unimportant decrease however the 95%CI also included clinically unimportant increases.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	
Single PSA test using a threshold of 3 ng/mL at age 50-69 years			
Risk of bias	No serious concerns	For the single trial reporting on this protocol, the CAP trial, there was a high risk of bias as it not possible to conceal the allocation of practices however this was not considered likely to cause major distortions to the results	*HIGH*
Indirectness	No serious concerns	Participants were men routinely attending participating primary care practices. PSA testing prior to randomisation not reported however estimates of any PSA testing in the control arm over 10 years were less than 20%. Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	No serious concerns	Based on a rate ratio at 15 years of 0.92 with a 95% confidence interval of 0.85 to 0.99, in a population of 10,000 men a single PSA test using a threshold of 3 ng/ml starting at ages 50-69 years is estimated to result in 6 fewer (12 fewer to 1 fewer) prostate cancer deaths when compared with usual care.	

		Using a MCID of 15 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 30 prostate cancer deaths per 10,000 and 60 prostate cancer deaths per 10,000, the absolute difference between the two arms was a clinically unimportant decrease with the confidence interval not crossing any thresholds.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	
PSA testing using thresholds of primarily of 3-4 ng/mL primarily every 4 years starting at ages 55-69 and ceasing primarily at age 74			
Risk of bias	No serious concerns	For the ERSPC trials incorporating results from 7 countries, no sources of bias likely to cause major distortions to the results were identified.	*MODERATE*
Indirectness	No serious concerns	Participants were identified from population registers. PSA testing prior to randomisation was not reported for most centres. PSA testing was not common in Europe in the 1990s so assume only a small proportion had undergone PSA testing prior to enrolment (1991-2003). Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	Serious concerns as to whether a clinically important decrease	Based on a rate ratio at 16 years of 0.80 with a 95% confidence interval of 0.72 to 0.89, in a population of 10,000 men PSA testing using thresholds of primarily of 3-4 ng/mL primarily every 4 years starting at ages 55-69 years and ceasing primarily after age 74 years is estimated to result in 18 fewer (25 fewer to 10 fewer) prostate cancer deaths when compared with usual care. Using a MCID of 16 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 32 prostate cancer deaths per 10,000 and 64 prostate cancer deaths per 10,000, the absolute difference between the two arms was a small clinically important decrease however the 95%CI crossed the threshold for trivial effects.	
Inconsistency	No serious concerns	The results are derived from 7 different centres. Trials at each centre were not individually powered to identify statistically significant differences. Results from 5 of the 6 centres with at least 14 years follow-up reported a decrease in prostate cancer mortality (See results for individual centres below). Differences in the magnitude of the effect can likely be explained by differences in the PSA testing protocols used, compliance rates and contamination rates.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	
PSA testing using thresholds of 3-10 ng/mL *(plus DRE and TRUS for first 6 years)* ***every 4-7 years starting at ages 55-69 and ceasing after 3 screens or age 74***			
Risk of bias	No serious concerns	For the single trial reporting on this protocol, the ERSPC Belgian centre, no sources of bias likely to cause major distortions to the results were identified.	*LOW*
Indirectness	No serious concerns	Participants were identified from population registers. PSA testing prior to randomisation was not reported. Men in control were referred to own GP for routine check-up which could include DRE as this was considered general practice for older men in Belgium. PSA testing was not common in Europe in the 1990s so assume only a small proportion had undergone PSA testing prior to enrolment (1991-2003). Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	Very serious concerns as to whether a clinically important decrease Extremely serious concerns as to whether a	Based on a rate ratio at 16 years of 0.78 with a 95% confidence interval of 0.44 to 1.34, in a population of 10,000 men PSA testing using thresholds of 3, 4 or 10 ng/mL every 4-7 years starting at ages 55-69 years and ceasing after age 74 years or 3 tests is estimated to result in 20 fewer (50 fewer to 30 more) prostate cancer deaths when compared with usual care. Using a MCID of 16 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 32 prostate cancer deaths per 10,000 and 64 prostate cancer deaths per 10,000, the absolute	

	small clinically important decrease	difference between the two arms was a small clinically important decrease however the 95%CI crossed the threshold for trivial effects and a small increase as well as a moderate decrease.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	
PSA testing using a threshold of 4 ng/mL every 4 years *(with triage test if PSA 3.0-3.9 ng/mL)* ***starting at ages 55, 59, 63 and 67 and ceasing after 3 screens or age 71***			
Risk of bias	No serious concerns	For the single trial reporting on this protocol, the ERSPC Finnish centres, no sources of bias likely to cause major distortions to the results were identified.	*MODERATE*
Indirectness	No serious concerns	Participants were identified from population registers. Only 0.7% of participants had undergone PSA testing prior to randomisation. Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	Serious concerns as to whether a clinically unimportant decrease	Based on a rate ratio at 16 years of 0.91 with a 95% confidence interval of 0.77 to 1.06, in a population of 10,000 men PSA testing using a threshold of 4 ng/mL every 4 years (with triage test if PSA 3.0-3.9 ng/mL) starting at ages 55, 59, 63 or 67 years and ceasing after age 71 years or 3 tests is estimated to result in 8 fewer (21 fewer to 5 more) prostate cancer deaths when compared with usual care. Using a MCID of 16 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 32 prostate cancer deaths per 10,000 and 64 prostate cancer deaths per 10,000, the absolute difference between the two arms was a clinically unimportant decrease however the 95%CI crossed the threshold for a small clinically important decrease.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	
PSA testing using a threshold of 4 ng/mL every 4 years *(with triage test if PSA 2.5-3.9 ng/mL)* ***starting at ages 55-69 and ceasing after age 74***			
Risk of bias	No serious concerns	For the single trial reporting on this protocol, the ERSPC Italian centre, no sources of bias likely to cause major distortions to the results were identified.	*VERY LOW*
Indirectness	No serious concerns	Participants were identified from population registers. PSA testing prior to randomisation was not reported. PSA testing was not common in Europe in the 1990s so assume only a small proportion had undergone PSA testing prior to enrolment (1996-2000). Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	Extremely serious concerns as to whether a clinically unimportant decrease	Based on a rate ratio at 16 years of 0.99 with a 95% confidence interval of 0.66 to 1.49, in a population of 10,000 men PSA testing using a threshold of 4 ng/mL every 4 years (with triage test if PSA 2.5-3.9 ng/mL) starting at ages 55-69 years and ceasing after age 74 years is estimated to result in 1 fewer (30 fewer to 44 more) prostate cancer deaths when compared with usual care. Using a MCID of 16 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 32 prostate cancer deaths per 10,000 and 64 prostate cancer deaths per 10,000, the absolute difference between the two arms was clinically unimportant however the 95%CI crossed the threshold for small and moderate increases as well as a small decrease.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	

PSA testing using thresholds of 3 or 4 ng/mL *(plus DRE and TRUS for first 3 years and triage if PSA 1.0-3.9 for the next 2 years)* ***every 4 years starting at ages 55-69 and ceasing after age 74 years***			
Risk of bias	No serious concerns	For the single trial reporting on this protocol, the ERSPC Netherlands centre, no sources of bias likely to likely to cause major distortions to the results were identified.	*MODERATE*
Indirectness	No serious concerns	Participants were identified from population registers. A small proportion (approximately 13%) of participants had undergone PSA testing (for any reason?) prior to randomisation. Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	Serious concerns as to whether a clinically important decrease at 16 and 21 years Very serious concerns as to whether a small clinically important decrease at 16 years Very serious concerns as to whether a moderate clinically important decrease at 21 years	Based on a rate ratio at 16 years of 0.67 with a 95% confidence interval of 0.53 to 0.85, in a population of 10,000 men, PSA testing using a threshold of 3 ng/mL or 4 ng/mL (with triage if PSA 1.0-3.9) every 4 years starting at ages 55-69 years and ceasing after age 74 years is estimated to result in 29 fewer (42 fewer to 13 fewer) prostate cancer deaths when compared with usual care. Using a MCID of 16 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 32 prostate cancer deaths per 10,000 and 64 prostate cancer deaths per 10,000, the absolute difference between the two arms was a small clinically important decrease however the 95%CI crossed the thresholds for moderate and trivial decreases. Based on a rate ratio at 21 years of 0.73 with a 95% confidence interval of 0.61 to 0.88, in a population of 10,000 men, PSA testing using a threshold of 3 ng/mL or 4 ng/mL (with triage if PSA 1.0-3.9) every 4 years starting at ages 55-69 years and ceasing after age 74 years is estimated to result in 43 fewer (62 fewer to 19 fewer) prostate cancer deaths when compared with usual care. Using a MCID of 21 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 42 prostate cancer deaths per 10,000 and 84 prostate cancer deaths per 10,000, the absolute difference between the two arms was a moderate clinically important decrease however the 95%CI crossed the thresholds for small and trivial decreases.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	
PSA testing using a threshold of 3 ng/mL every 4 years starting at ages 55-69 and ceasing after 3 screens or age 74			
Risk of bias	No serious concerns	For the single trial reporting on this protocol, the ERSPC Spanish centre, no sources of bias likely to likely to cause major distortions to the results were identified.	*VERY LOW*
Indirectness	No serious concerns	Participants were identified from population registers. PSA testing prior to randomisation was not reported. PSA testing was not common in Europe in the 1990s so assume only a small proportion had undergone PSA testing prior to enrolment (1996-1999). Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	Extremely serious concerns as to whether a clinically important decrease	Based on a rate ratio at 16 years of 0.65 with a 95% confidence interval of 0.13 to 2.63, in a population of 10,000 men PSA testing using a threshold of 3 ng/mL every 4 years starting at ages 55-69 years and ceasing after 3 screens or age 74 years is estimated to result in 31 fewer (78 fewer to 145 more) prostate cancer deaths when compared with usual care. Using a MCID of 16 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 32 prostate cancer deaths per 10,000 and 64 prostate cancer deaths per 10,000, the absolute difference between the two arms was a small clinically important decrease however the 95%CI crossed the thresholds for small, moderate and large increases as well as moderate and large decreases.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	

Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	
PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 55-64 and ceasing after age 69			
Risk of bias	No serious concerns	For the single trial reporting on this protocol, the ERSPC Swedish centre (Goteborg trial), no sources of bias likely to likely to cause major distortions to the results were identified.	*MODERATE*
Indirectness	No serious concerns	Participants were identified from population registers. A small proportion (approximately 4.2-4.6%) of participants in the entire cohort aged 50-64 years had undergone PSA testing (for any reason?) prior to randomisation. Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	Serious concerns as to whether a clinically important decrease Very serious concerns as to whether a moderate clinically important decrease	Based on a rate ratio at 16 years of 0.63 with a 95% confidence interval of 0.44 to 0.88, in a population of 10,000 men PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 55-69 years and ceasing after age 69 years is estimated to result in 33 fewer (50 fewer to 11 fewer) prostate cancer deaths when compared with usual care. Using a MCID of 16 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 32 prostate cancer deaths per 10,000 and 64 prostate cancer deaths per 10,000, the absolute difference between the two arms was a moderate clinically important decrease however the 95%CI crossed the thresholds for small and trivial decreases.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	
PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 50-64 and ceasing after age 69			
Risk of bias	No serious concerns	For the single trial reporting on this protocol, the ERSPC Swedish centre (Goteborg trial), no sources of bias likely to likely to cause major distortions to the results were identified.	*HIGH* *for 14- and 18-year prostate cancer mortality* *MODERATE* *for 22-year prostate cancer mortality*
Indirectness	No serious concerns	Participants were identified from population registers. A small proportion (approximately 4.2-4.6%) of participants aged 50-64 years had undergone PSA testing (for any reason?) prior to randomisation. Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	No serious concerns as to whether a clinically important decrease at 14 and 18 years Serious concerns as to whether a clinically important decrease at 22 years Serious concerns as to whether clinically important decrease is moderate at 14 years Very serious concerns as to whether clinically important decrease is moderate at 18 years	Based on a rate ratio at 14 years of 0.56 with a 95% confidence interval of 0.39 to 0.82, in a population of 10,000 men PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 50-64 years and ceasing after age 69 years is estimated to result in 40 fewer (55 fewer to 16 fewer) prostate cancer deaths when compared with usual care. Using a MCID of 14 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 28 prostate cancer deaths per 10,000 and 56 prostate cancer deaths per 10,000, the absolute difference between the two arms was a moderate clinically important decrease however the 95%CI crossed the threshold for a small decrease but not a trivial decrease. Based on a rate ratio at 18 years of 0.65 with a 95% confidence interval of 0.49 to 0.87, in a population of 10,000 men PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 50-64 years and ceasing after age 69 years is estimated to result in 53 fewer (77 fewer to 20 fewer) prostate cancer deaths when compared with usual care. Using a MCID of 18 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 36 prostate cancer deaths per 10,000 and 72 prostate cancer deaths per 10,000, the absolute difference between the two arms was a moderate clinically important decrease however the 95%CI crossed the thresholds for small and large decreases but not a trivial decrease.	

	Extremely serious concerns as to whether decrease is moderate at 22 years	Based on a rate ratio at 22 years of 0.71 with a 95% confidence interval of 0.55 to 0.91, in a population of 10,000 men PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 50-64 years and ceasing after age 69 years is estimated to result in 62 fewer (96 fewer to 19 fewer) prostate cancer deaths when compared with usual care. Using a MCID of 22 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 44 prostate cancer deaths per 10,000 and 88 prostate cancer deaths per 10,000, the absolute difference between the two arms was a moderate clinically important decrease however the 95%CI crossed the thresholds clinically unimportant decreases as well as small and large decreases.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	

CAP = Cluster Randomized Trial of PSA testing for Prostate Cancer; CI = confidence interval; DRE = digital rectal examination; ERSPC = European Randomised Study of Screening for Prostate Cancer; MCID = minimal clinically important difference; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA = prostate specific antigen; RR = rate ratio or risk ratio; TRUS = transrectal ultrasound

Table 9. *GRADE assessment of the certainty of the evidence for metastases at diagnosis or on progression from randomised controlled trials comparing a PSA testing protocol with usual care in an average risk population*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Annual PSA testing using a threshold of 4 ng/mL for 6 years + annual DRE for 4 years starting at age 55-74 years			
Risk of bias	Serious concerns	For the single trial reporting on this protocol, the PLCO trial, the risk of bias due to deviations from intended interventions was considered high with 46% of those in the usual care arm receiving a PSA test as part of routine health check-up in the past year during the first 6 years of the trial likely leading to the underestimation of the effects of the intervention.	*LOW*
Indirectness	Serious concerns	Approximately 50% of participants had received a PSA test in the 3 years prior to enrolment. In addition, participants were recruited by 10 tertiary care institutions rather than the general population. Consequently, the results may not be directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	No serious concerns	Based on a rate ratio at 15 years of 0.98 with a 95% confidence interval of 0.81 to 1.18, in a population of 10,000 men annual PSA testing for 6 years using a threshold of 4 ng/mL starting at ages 55-74 years plus an annual DRE for the first 4 years is estimated to result in 2 fewer (15 fewer to 15 more) metastases at diagnosis or on progression when compared with usual care. Using a MCID of 30 metastases cases per 10,000 men and thresholds for moderate and large effects of 60 metastases cases per 10,000 and 120 metastases cases per 10,000, the absolute difference between the two arms was a clinically unimportant decrease however the 95%CI also included clinically unimportant increases.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	

PSA testing using thresholds of primarily of 3-4 ng/mL primarily every 4 years starting at ages 55-69 and ceasing primarily at age 74			
Risk of bias	No serious concerns	For the ERSPC trials incorporating results from 4 centres in 4 countries, no sources of bias likely to cause major distortions to the results were identified.	*MODERATE*
Indirectness	No serious concerns	Participants were identified from population registers. PSA testing prior to randomisation was not reported for most centres. PSA testing was not common in Europe in the 1990s so assume only a small proportion had undergone PSA testing prior to enrolment (1993-2003). Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	Serious concerns as to whether a clinically important decrease	Based on a rate ratio at 12 years of 0.70 with a 95% confidence interval of 0.60 to 0.82, in a population of 10,000 men PSA testing using thresholds of primarily of 3-4 ng/mL primarily every 4 years starting at ages 55-69 years and ceasing primarily after age 74 years is estimated to result in 31 fewer (42 fewer to 19 fewer) metastases at diagnosis or on progression when compared with usual care. Using a MCID of 24 cases of metastases per 10,000 men and thresholds for moderate and large effects of 48 metastases cases per 10,000 and 96 metastases cases per 10,000, the absolute difference between the two arms was a small clinically important decrease however the 95%CI crossed the threshold for trivial effects.	
Inconsistency	Not Assessable	Inconsistency was not assessable. The results are derived from 4 different centres however results were not reported for the individual centres.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	
PSA testing using thresholds of 3 or 4 ng/mL *(plus DRE and TRUS for first 3 years and triage if PSA 1.0-3.9 for the next 2 years)* ***every 4 years starting at ages 55-69 and ceasing after age 74 years***			
Risk of bias	No serious concerns	For the single trial reporting on this protocol, the ERSPC Netherlands centre, no sources of bias likely to likely to cause major distortions to the results were identified.	*HIGH*
Indirectness	No serious concerns	Participants were identified from population registers. A small proportion (approximately 13%) of participants had undergone PSA testing (for any reason?) prior to randomisation. Consequently, the results likely directly relevant to an unscreened primarily average risk population in the primary care setting.	
Imprecision	No serious concerns	Based on a rate ratio at 21 years of 0.67 with a 95% confidence interval of 0.58 to 0.78, in a population of 10,000 men, PSA testing using a threshold of 3 ng/mL or 4 ng/mL (with triage if PSA 1.0-3.9) every 4 years starting at ages 55-69 years and ceasing after age 74 years is estimated to result in 115 fewer (147 fewer to 77 fewer) metastases at diagnosis or on progression when compared with usual care. Using a MCID of 42 cases of metastases per 10,000 men and thresholds for moderate and large effects of 84 metastases cases per 10,000 and 168 metastases cases per 10,000, the absolute difference between the two arms was a moderate clinically important decrease however the 95%CI crossed the threshold for a small but not a trivial decrease.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Not detected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	

CI = confidence interval; DRE = digital rectal examination; ERSPC = European Randomised Study of Screening for Prostate Cancer; MCID = minimal clinically important difference; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA = prostate specific antigen; RR = rate ratio or risk ratio; TRUS = transrectal ultrasound

4. Summary of findings

Table 10. *Summary of findings for randomised controlled trials comparing a PSA testing protocol/PSA testing protocols with usual care in average risk populations*

Outcome (MCID)	*Time frame*	*RCTs (Participants)*	*PSA testing protocol*	*Study results and measurements*	*Absolute effect estimates per 10,000*				*Certainty of evidence (GRADE)*	*Plain text summary*
					Metric	*Usual care*	*PSA testing (95% CI)*	*Absolute difference (95% CI)*		
14–18-year prostate cancer mortality										
Annual PSA testing using threshold of 4 ng/mL for 6 years + annual DRE for 4 years starting at age 55-74 years										
Prostate cancer mortality (16/10,000)	16 years	1 (76,683)	PSA cut-off: **4** ng/mL Test interval: **1** year Starting age **55-74** years Ceasing after **6** years + *annual DRE for 4 years*	RR = 0.93 (95%CI: 0.81-1.08)	Prostate cancer deaths per 10,000	62.3	57.9 (50.5-67.3)	4 fewer (12 fewer to 5 more)	Low[1]	In a population of asymptomatic men annual PSA testing using a threshold of 4 ng/mL for 6 years starting at ages 55 to 74 plus annual DRE for the first 4 years may result in a **clinically unimportant^** difference in prostate cancer mortality at 16 years when compared with usual care.
Single PSA test using threshold of 3 ng/mL at ages 50-69 years										
Prostate cancer mortality (15/10,000)	15 years	1 (415,357)	Single PSA test PSA cut-off: **3** ng/mL Test interval: **0** year Starting age **50-69** years	RR = 0.92 (95%CI: 0.85 -0.99)	Prostate cancer deaths per 10,000	78	72 (66 – 77)	6 fewer (12 fewer to 1 fewer)	High	In a population of asymptomatic men a single PSA test using a threshold of 3 ng/mL at ages 50 to 69 results in a **clinically unimportant*** decrease in prostate cancer mortality at 15 years when compared with usual care.
PSA testing using thresholds of primarily of 3-4 ng/mL primarily every 4 years starting at ages 55-69 and ceasing primarily at age 74										
Prostate cancer mortality (16/10,000)	16 years	1 (162,241)	PSA cut-off: primarily **3 or 4** ng/mL Test interval: primarily **4** years Starting age **55-69** years Ceasing primarily after age **74**	RR = 0.80 (95%CI: 0.72-0.89)	Prostate cancer deaths per 10,000	89.2	71.4 (64.2-79.4)	18 fewer (25 fewer to 10 fewer)	Moderate[4]	In a population of asymptomatic men PSA testing using a threshold of primarily 3 or 4 ng/mL primarily every 4 years starting at ages 55-69 and ceasing primarily after age 74 probably results in a **clinically important (small)^** decrease in prostate cancer mortality at 16 years when compared with usual care
PSA testing using a threshold of 3-10 ng/mL *(plus DRE and TRUS for first 6 years)* ***every 4-7 years starting at ages 55-69 and ceasing after 3 screens or age 74***										

Prostate cancer mortality (16/10,000)	16 years	1 (8562)	PSA cut-off: **3, 4 and 10** ng/mL Test interval: **4-7** years Starting age **55-69** years Ceasing after age **74 or 3 screens** + *DRE and TRUS for first 6 years*	RR = 0.78 (95%CI: 0.44-1.34)	Prostate cancer deaths per 10,000	89.2	69.6 (39.2-119.5)	20 fewer (50 fewer to 30 more)	Low[2]	In a population of asymptomatic men PSA testing using a threshold of 3-10 ng/mL every 4-7 years starting at ages 55-69 and ceasing after 3 screens or age 74 may result in a **clinically important (small)^** decrease in prostate cancer mortality at 16 years when compared with usual care.
PSA testing using a threshold of 4 ng/mL every 4 years *(with triage test if PSA 3.0-3.9 ng/mL)* ***starting at ages 55, 59, 63 and 67 and ceasing after 3 screens or age 71***										
Prostate cancer mortality (16/10,000)	16 years	1 (80,379)	PSA cut-off: **4** ng/mL Test interval: **4** years Starting age **55, 59, 63 and 67** years Ceasing after age **71 or 3 screens** + *Triage test if PSA 3.0-3.9 ng/mL*	RR = 0.91 (95%CI: 0.77-1.06)	Prostate cancer deaths per 10,000	89.2	81.2 (68.7-94.6)	8 fewer (21 fewer to 5 more)	Moderate[4]	In a population of asymptomatic men PSA testing using a threshold of 4 ng/mL every 4 years (with triage test if PSA 3.0-3.9 ng/mL) starting at ages 55, 59, 63 and 67 and ceasing after 3 screens or age 71 probably results in a trivial **clinically unimportant^** decrease in prostate cancer mortality at 16 years when compared with usual care
PSA testing using a threshold of 4 ng/mL every 4 years *(with triage test if PSA 2.5-3.9 ng/mL)* ***starting at ages 55-69 and ceasing after age 74***										
Prostate cancer mortality (16/10,000)	16 years	1 (14,515)	PSA cut-off: **4** ng/mL Test interval: **4** years Starting age **55-69** years Ceasing after age **74** + *Triage test if PSA 2.5-3.9 ng/mL*	RR = 0.99 (95%CI: 0.66-1.49)	Prostate cancer deaths per 10,000	89.2	88.3 (58.9-132.9)	1 fewer (30 fewer to 44 more)	Very low[3]	In a population of asymptomatic men we are uncertain as to whether PSA testing using a threshold of 4 ng/mL every 4 years (with triage test if PSA 2.5-3.9 ng/mL) starting at ages 55-69 and ceasing after age 74 results in **no difference** in prostate cancer mortality at 16 years when compared with usual care
PSA testing using a threshold of 3-4 ng/mL *(plus DRE and TRUS for first 3 years and triage if PSA 1.0-3.9 for the next 2 years)* ***every 4 years starting at ages 55-69 and ceasing after age 74***										
Prostate cancer mortality (16/10,000)	16 years	1 (34,833)	PSA cut-off: **3-4** ng/mL Test interval: **4** years Starting age **55-69** years Ceasing after age **74** + *DRE and TRUS for first 3 years followed by triage test if PSA*	RR = 0.67 (95%CI: 0.53-0.85)	Prostate cancer deaths per 10,000	89.2	59.8 (47.3-75.8)	29 fewer (42 fewer to 13 fewer)	Moderate[4]	In a population of asymptomatic men PSA testing using a threshold of 3 or 4 ng/mL every 4 years starting at ages 55-69 and ceasing after age 74 probably results in a **clinically important (small)^** decrease in prostate cancer mortality at 16 years when compared with usual care

			1.0-3.9 for next 2 years							
PSA testing using a threshold of 3 ng/mL every 4 years starting at ages 55-69 and ceasing after 3 screens or age 74										
Prostate cancer mortality (16/10,000)	16 years	1 (2197)	PSA cut-off: **3** ng/mL Test interval: **4** years Starting age **55-69** years Ceasing after 3 screens or age **74**	RR = 0.65 (95%CI: 0.13-2.63)	Prostate cancer deaths per 10,000	89.2	58.0 (11.6-234.6)	31 fewer (78 fewer to 145 more)	Very low[3]	In a population of asymptomatic men we are uncertain as to whether PSA testing using a threshold of 3 ng/mL every 4 years starting at ages 55-69 and ceasing after age 74 or 3 screens results in a **clinically important (small)**^ decrease in prostate cancer mortality at 16 years when compared with usual care
PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 55-64 and ceasing after age 69										
Prostate cancer mortality (16/10,000)	16 years	1 (11,852)	PSA cut-off: 2.5-3.4 ng/mL Test interval: **2** years Starting age **55-64** years Ceasing after age 69	RR = 0.63 (95%CI: 0.44-0.88)	Prostate cancer deaths per 10,000	89.2	56.2 (39.2-78.5)	33 fewer (50 fewer to 11 fewer)	Moderate[4]	In a population of asymptomatic men PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 55-64 and ceasing after age 69 probably results in **a clinically important (moderate**)^ decrease in prostate cancer mortality at 16 years when compared with usual care
PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 50-64 and ceasing after age 69										
(14/10,000)	14 years	1 (19,904)	PSA cut-off: 2.5-3.4 ng/mL Test interval: **2** years Starting age **50-64** years Ceasing after age 69	RR = 0.56 (95%CI: 0.39-0.82)	Prostate cancer deaths per 10,000	90	50.4 (35.1-73.8)	40 fewer (55 fewer to 16 fewer)	High	In a population of asymptomatic men PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 50-64 and ceasing after age 69 results in a **clinically important (moderate)**** ^^ decrease in prostate cancer mortality at 14 and 18 years when compared with usual care
(18/10,000)	18 years	1 (19,899)		RR = 0.65 (95%CI: 0.49-0.87)		150	97.5 (73.5-130.5)	53 fewer (77 fewer to 20 fewer)	High	
21-22-year prostate cancer mortality										
PSA testing using a threshold of 3-4 ng/mL *(plus DRE and TRUS for first 3 years and triage if PSA 1.0-3.9 for the next 2 years)* ***every 4 years starting at ages 55-69 and ceasing after age 74***										
Prostate cancer mortality (21/10,000)	21 years	1 (34,833)	PSA cut-off: **3-4** ng/mL Test interval: **4** years Starting age **55-69** years Ceasing after age **74** +	RR = 0.73 (95%CI: 0.61-0.88)	Prostate cancer deaths per 10,000	159	116.1 (97.0-139.9)	43 fewer (62 fewer to 19 fewer)	Moderate[4]	In a population of asymptomatic men PSA testing using a threshold of 3 or 4 ng/mL every 4 years starting at ages 55-69 and ceasing after age 74 probably results in a **clinically important (moderate)*^** decrease in prostate cancer

			DRE and TRUS for first 3 years followed by triage test if PSA 1.0-3.9 for next 2 years							mortality at 21 years when compared with usual care
PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 50-64 and ceasing after age 69										
Prostate cancer mortality (22/10,000)	22 years	1 (19,894)	PSA cut-off: 2.5-3.4 ng/mL Test interval: **2** years Starting age **50-64** years Ceasing after age 69	RR = 0.71 (95%CI: 0.55-0.91)	Prostate cancer deaths per 10,000	213	151.2 (117.2-193.8)	62 fewer (96 fewer to 19 fewer)	Moderate[4]	In a population of asymptomatic men PSA testing using thresholds of 2.5-3.4 ng/mL every 2 years starting at ages 50-64 and ceasing after age 69 probably results in a **clinically important (moderate)**^* decrease in prostate cancer mortality at 22 years when compared with usual care
Metastases at diagnosis or on progression										
Annual PSA testing using threshold of 4 ng/mL for 6 years + annual DRE for 4 years starting at age 55-74 years										
Metastases at diagnosis or on progression (30/10,000)	15 years	1 (76,683)	PSA cut-off: **4** ng/mL Test interval: **1** year Starting age **55-74** years Ceasing after **6** years + *annual DRE for 4 years*	RR = 0.98 (95%CI: 0.81-1.18)	Metastases at diagnosis or on progression per 10,000	80	78 (65-95)	2 fewer (15 fewer to 15 more)	Low[1]	In a population of asymptomatic men annual PSA testing using a threshold of 4 ng/ml for 6 years starting at ages 55 to 74 plus annual DRE for the first 4 years may result in a **clinically unimportant**^^ difference in metastases at diagnosis or on progression at 15 years when compared with usual care.
PSA testing using thresholds of primarily of 3-4 ng/mL primarily every 4 years starting at ages 55-69 and ceasing primarily at age 74										
Metastases at diagnosis or on progression (24/10,000)	12 years	1 (76,813)	PSA cut-off: primarily **3 or 4** ng/mL Test interval: primarily **4** years Starting age **55-69** years Ceasing primarily after age **74**	RR = 0.70 (95%CI: 0.60-0.82)	Metastases at diagnosis or on progression per 10,000	104	72.8 (62.4-85.3)	31 fewer (42 fewer to 19 fewer)	Moderate[4]	In a population of asymptomatic men PSA testing using a threshold of primarily 3 or 4 ng/mL primarily every 4 years starting at ages 55-69 and ceasing primarily after age 74 probably results in a **clinically important (small)**^^* decrease in metastases at diagnosis or on progression at 12 years when compared with usual care
PSA testing using a threshold of 3 or 4 ng/mL *(plus DRE and TRUS for first 3 years and triage if PSA 1.0-3.9 for the next 2 years)* ***every 4 years starting at ages 55-69 and ceasing after 3 screens or age 74***										
Metastases at diagnosis or on progression	21 years	1 (34,833)	PSA cut-off: **3-4** ng/mL Test interval: **4** years	RR = 0.67 (95%CI: 0.58-0.78)	Metastases at diagnosis or on	349	233.8 (202.4-272.2)	115 fewer (147 fewer to 77 fewer)	High	In a population of asymptomatic men PSA testing using a threshold of 3 or 4 ng/mL every 4 years starting at ages 55-69

(42/10,000)			Starting age **55-69** years Ceasing after age **74** + *DRE and TRUS for first 3 years followed by triage test if PSA 1.0-3.9 for next 2 years*		progression per 10,000					and ceasing after age 74 results in a **clinically important (moderate)*^^** decrease in metastases at diagnosis or on progression at 21 years when compared with usual care

CI = confidence interval; DRE = digital rectal examination; MCID = minimally important difference; PSA = prostate specific antigen; RCT = randomised controlled trial; RR = rate or risk ratio; TRUS = transrectal ultrasound

[1] Downgraded by two levels due to concerns re risk of bias and indirectness

[2] Downgraded by two levels due to very serious concerns re imprecision

[3] Downgraded by three levels due to extremely serious concerns re imprecision

[4] Downgraded by one level due to serious concerns re imprecision

^ Using thresholds of 16, 32 and 64 prostate cancer deaths per 10,000 men at 16 years for small (minimal clinically important difference), moderate and large effects

** Using thresholds of 15, 30 and 60 prostate cancer deaths per 10,000 men at 15 years for small (minimal clinically important difference), moderate and large effects*

*** Using thresholds of 14, 28 and 56 prostate cancer deaths per 10,000 men at 14 years for small (minimal clinically important difference), moderate and large effects*

^^ Using thresholds of 18, 36 and 72 prostate cancer deaths per 10,000 men at 18 years for small (minimal clinically important difference), moderate and large effects

**^ Using thresholds of 21, 42 and 84 prostate cancer deaths per 10,000 men at 21 years for small (minimal clinically important difference), moderate and large effects*

^ Using thresholds of 22, 44 and 88 prostate cancer deaths per 10,000 men at 22 years for small (minimal clinically important difference), moderate and large effects*

***^ Using thresholds of 30, 60 and 120 metastases at diagnosis or on progression per 10,000 men at 15 years for small (minimal clinically important difference), moderate and large effects*

^^* Using thresholds of 24, 48 and 96 metastases at diagnosis or on progression per 10,000 men at 12 years for small (minimal clinically important difference), moderate and large effects

**^^ Using thresholds of 42, 84 and 168 metastases at diagnosis or on progression per 10,000 men at 21 years for small (minimal clinically important difference), moderate and large effects*

5. Ongoing clinical trials

Three potentially relevant ongoing trials were identified from literature searches, clinical trial registry searches or from recent guidelines, and are described in Table 11.

Table 11. *Summary of potentially relevant ongoing randomised controlled trials comparing a PSA testing protocol with usual care in an average risk population*

Study ID	Study name, location and study design	Start date	Planned completion date	Status	Population	Intervention	Comparator	Outcomes
NCT03423303	A Randomized Trial of Early Detection of Clinically Significant Prostate Cancer (ProScreen) Finland RCT – 2 arms	2018	2032	Active, not recruiting	Men aged 50-63 years in 2018	Prostate cancer screening – frequency dependent on previous PSA level PSA ≥ 3 ng/mL, undergo 4kScore triage to mpMRI If MRI-positive – targeted biopsies If MRI-negative- systematic biopsy only if PSAD > 0.15	Usual care	*Primary* 10-year Prostate cancer mortality
ISRCTN94604465	Goteborg Prostate Cancer Screening 2 Trial (Goteborg-2) Sweden RCT – 4 arms	2015	2040	Ongoing	Men aged 50-60 years	PSA testing – frequency dependent on previous PSA level Arm 1: If PSA ≥ 3.0 ng/mL standard biopsy regardless of MRI result + targeted biopsy for MRI positive Arm 2: If PSA ≥ 3.0 ng/mL undergo mpMRI If MRI-positive MRI-targeted biopsies only Arm 3: If PSA ≥ 1.8 ng/mL undergo mpMRI If MRI positive undergo targeted biopsy	Usual care	*Primary* Clinically insignificant cancer (Gleason score 3+3) *Secondary* Clinically significant cancer (Gleason score ≥ 3+4) Prostate cancer mortality for screened vs no screened at 12 years and then every 3 years
ISRCTN37591328	PROBASE Germany RCT – 2 arms	2014	2034?	Active, not recruiting	Men aged 45 years	Immediate PSA stratified PSA screening	Immediate offer of DRE only PSA stratified PSA screening starting at age 50	Prostate cancer detection *At age 60* • Metastases • Metastases after treatment • Prostate cancer mortality • Overall survival

DRE = digital rectal examination; mpMRI = multiparametric MRI; PSA = prostate-specific antigen; PSAD = prostate-specific antigen density; RCT = randomised controlled trial

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APPENDICES

Appendix A: Literature search strategies

A.1 Search strategies used for the 2016 guidelines

Database: Medline

#	*Search terms*
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	prostate-specific antigen/
5	prostate specific antigen.tw,mp.
6	PSA.mp,tw.
7	4 or 5 or 6
8	exp mass screening/
9	"early detection of cancer"/
10	screen$.mp,tw.
11	8 or 9 or 10
12	clinical trial.pt.
13	random$.mp.
14	((single or double) adj3 (blind$ or mask$)).mp,tw.
15	placebo$.mp,tw.
16	12 or 13 or 14 or 15
17	3 and 7 and 11 and 16
18	limit 17 to (english language and humans and yr="2012-current")

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b). Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report. Canberra: National Health and Medical Research Council.

Aboriginal and Torres Strait Island related search terms used

#	*Search terms*
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

Database: Embase

#	*Search terms*
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp
3	1 OR 2
4	'prostate specific antigen'/exp
5	'prostate specific antigen':de,ab,ti OR psa:de,ab,ti
6	'prostate specific antigen' OR psa
7	4 OR 5 OR 6
8	'mass screening'/exp
9	'screening test'/exp
10	'early diagnosis'/exp
11	screen*

12	8 OR 9 OR 10 OR 11
13	'clinical trial'
14	'clinical trial':de
15	random*
16	random*:ab,ti
17	(single OR double) NEAR/3 (blind* OR mask*)
18	((single OR double) NEAR/3 (blind* OR mask*)):ab,ti
19	placebo*
20	placebo:ab,ti
21	13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22	[embase]/lim AND [2012-2014]/py AND [english]/lim AND [humans]/lim
23	3 AND 7 AND 12 AND 21 AND 22

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b). Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report. Canberra: National Health and Medical Research Council.

Aboriginal and Torres Strait Island related search terms used

#	***Search terms***
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

Database: CENTRAL

#	***Search terms***
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	Prostate-Specific Antigen/
5	prostate specific antigen.tw,mp.
6	psa.tw,mp.
7	4 or 5 or 6
8	exp mass screening/
9	"early detection of cancer"/
10	screen$.mp,tw.
11	8 or 9 or 10
12	clinical trial.pt.
13	random$.mp.
14	((single or double) adj3 (blind$ or mask$)).mp,tw.
15	placebo$.mp,tw.
16	12 or 13 or 14 or 15
17	3 and 7 and 11 and 16
18	limit 17 to (yr="2012-current")

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b).
For Cochrane Database of Systematic Reviews – The Cochrane Library: Title, abstracts, keywords: “prostate”

Database: Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP)

#	*Search terms*
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

A.2 Search strategies used to identify articles published 2019 onwards

Databases: Medline and Embase database (via Ovid platform)

#	*Search terms*
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).tw.
3	1 or 2
4	exp prostate-specific antigen/
5	prostate specific antigen.tw.
6	PSA.tw.
7	4 or 5 or 6
8	exp mass screening/
9	exp “early detection of cancer”/
10	8 or 9
11	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
12	Randomized Controlled Trial/
13	exp Randomized Controlled Trials as Topic/
14	“Randomized Controlled Trial (topic)”/
15	Controlled Clinical Trial/
16	exp Controlled Clinical Trials as Topic/
17	“Controlled Clinical Trial (topic)”/
18	Randomization/
19	Random Allocation/
20	Double-Blind Method/
21	Double Blind Procedure/
22	Double-Blind Studies/
23	Single-Blind Method/
24	Single Blind Procedure/
25	Single-Blind Studies/
26	Placebos/
27	Placebo/
28	Control Groups/
29	Control Group/
30	(random* or sham or placebo*).ti,ab,hw,kf.
31	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
32	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
33	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
34	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
35	allocated.ti,ab,hw.

36	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
37	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
38	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
39	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
40	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
41	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
42	or/11-41
43	3 and 7 and 10 and 42
44	limit 43 to (english language and humans and yr="2019-current")

Includes RCT / CCT - MEDLINE, Embase search filter. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 30/11/2023.

Database: Cochrane Central Register of Controlled Trials

#	***Search terms***
1	*exp Prostatic Neoplasms/*
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).tw.
3	1 or 2
4	exp prostate-specific antigen/
5	prostate specific antigen.tw.
6	PSA.tw.
7	4 or 5 or 6
8	exp mass screening/
9	exp "early detection of cancer"/
10	8 or 9
11	3 and 7 and 10
12	limit 11 to (english language and humans and yr="2019-current")

Appendix B: GRADE assessment of the certainty of the evidence

Grade	***Definition***
⊕⊕⊕⊕ High certainty	We are very confident that the true effect lies close to that of the estimate of the effect.
⊕⊕⊕◯ Moderate certainty	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ Low certainty	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
⊕◯◯◯ Very low certainty	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reportedly based on systematic reviews

Developer	***Publication or link***	***Title***	***Year***	***Reasons for not adopting***
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Systematic reviews of the evidence were not accessible.

Prostate Cancer Foundation (USA)	Garroway et al. 2024 https://www.doi.org/10.1056/EVIDoa2300289	Prostate Cancer Foundation Screening Guidelines for Black Men in the United States	2024	Systematic reviews of the evidence were not accessible and the reported systematic review methods did not mention risk of bias or GRADE assessments. Not directly relevant.

Appendix D: Excluded articles – 2016 guidelines searches

Article	*Reason for exclusion*
Andriole 2012	No relevant outcomes
Andriole 2009	Superseded
Andriole 2005	No comparative data
Aus 2007	Superseded
Bokhorst 2014	Superseded
Carlsson 2011	No population of interest
Crawford 2011	Superseded
Djulbegovic 2010	Superseded
Grenabo Bergdahl 2013	Superseded
Grenabo Bergdahl 2009	No comparative data
Ilic 2013	Superseded
Johnson 2006	No relevant outcomes
Kerkhof 2010	Superseded
Kilpelainen 2013	Superseded
Kilpelainen 2011	No relevant outcomes
Kilpelainen 2010	No relevant outcomes
Kjellman 2009	Ineligible intervention
Labrie 2004	No relevant outcomes
Lin 2011	Did not provide original or additional data for RCTs included for Q4.1
Lumen 2012	Superseded
New Zealand Guidelines Group 2009	Did not provide original or additional data for RCTs included for Q4.1
Pinsky 2012	No population of interest
Raaijmakers 2002	No comparative data
Roobol 2013	Superseded
Roobol 2009	Superseded
Sandblom 2011	Ineligible study design
Sandblom 2004	Ineligible study design
Schroder 2012	Superseded
Schroder 2009	Superseded
Taylor 2004	No relevant outcomes
Zhu 2011	No comparative data

References of excluded articles – 2016 guidelines

Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104(2):125-132.

Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360(13):1310-1319.

Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, Chia D et al. Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. J Natl Cancer Inst 2005; 97(6):433-438.

Aus G, Bergdahl S, Lodding P, Lilja H, Hugosson J. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol 2007; 51(3):659-664.

Bokhorst LP, Bangma CH, van Leenders GJ, Lous JJ, Moss SM, Schroder FH et al. Prostate-specific antigen-based prostate cancer screening: reduction of prostate cancer mortality after correction for nonattendance and contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2014; 65(2):329-336.

Carlsson SV, Holmberg E, Moss SM, Roobol MJ, Schroder FH, Tammela TL et al. No excess mortality after prostate biopsy: results from the European Randomized Study of Screening for Prostate Cancer. BJU Int 2011; 107(12):1912-1917.

Crawford DE, Grubb R, Black A, Andriole GL, Chen M-H, Izmirlian G et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. J Clin Oncol 2011; 29(4): 355-361.

Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, Djulbegovic B et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ 2010; 341:c4543.

Grenabo Bergdahl A, Holmberg E, Moss S, Hugosson J. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. Eur Urol 2013; 64(5):703-709.

Grenabo Bergdahl A, Aus G, Lilja H, Hugosson J. Risk of dying from prostate cancer in men randomized to screening: differences between attendees and nonattendees. Cancer 2009; 115(24):5672-5679.

Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013; 1:CD004720
.
Johnson DB. The effects of an abnormal cancer screening test on health related quality of life. International Journal of Cancer Research 2006; 2(3):277-289.

Kerkhof M, Roobol MJ, Cuzick J, Sasieni P, Roemeling S, Schroder FH et al. Effect of the correction for noncompliance and contamination on the estimated reduction of metastatic prostate cancer within a randomized screening trial (ERSPC section Rotterdam). Int J Cancer 2010; 127(11):2639-2644.

Kilpelainen TP, Tammela TL, Malila N, Hakama M, Santti H, Maattanen L et al. Prostate cancer mortality in the Finnish randomized screening trial. Journal of the National Cancer Institute 2013; 105(10):719-725.

Kilpelainen TP, Tammela TL, Roobol M, Hugosson J, Ciatto S, Nelen V et al. False-positive screening results in the European randomized study of screening for prostate cancer. Eur J Cancer 2011; 47(18):2698-2705.

Kilpelainen TP, Tammela TL, Maattanen L, Kujala P, Stenman UH, Ala-Opas M et al. False-positive screening results in the Finnish prostate cancer screening trial. Br J Cancer 2010; 102(3):469-474.

Kjellman A, Akre O, Norming U, Tornblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. J Urol 2009; 181(4):1615-1621.

Labrie F, Candas B, Cusan L, Gomez JL, Belanger A, Brousseau G et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate 2004; 59(3):311-318.

Lin K, Croswell JM, Koenig H, Lam C, Maltz A. Prostate-specific antigen-based screening for prostate cancer: an evidence update for the U.S. preventive services task force. Evidence synthesis no.90. 2011. Rockville, MD, Agency for Healthcare Research and Quality.

Lumen N, Fonteyne V, De MG, Ost P, Villeirs G, Mottrie A et al. Population screening for prostate cancer: an overview of available studies and meta-analysis. Int J Urol 2012; 19(2):100-108.

New Zealand Guidelines Group. Cancer control strategy guidance completion: update of evidence for prostate-specific antigen (PSA) testing in asymptomatic men. 2009. Wellington, Ministry of Health.

Pinsky PF, Black A, Parnes HL, Grubb R, David CE, Miller A et al. Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiol 2012; 36(6):e401-e406.

Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schroder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002; 60(5):826-830.

Roobol MJ, Kranse R, Bangma CH, Van Leenders AGJL, Blijenberg BG, Van Schaik RHN et al. Screening for prostate cancer: Results of the Rotterdam section of the European randomized study of screening for prostate cancer. Eur Urol 2013; 64(4):530-539.

Roobol MJ, Kerkhof M, Schroder FH, Cuzick J, Sasieni P, Hakama M et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2009; 56(4):584-591.

Sandblom G, Varenhorst E, Rosell J, Lofman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. BMJ 2011; 342:d1539.

Sandblom G, Varenhorst E, Lofman O, Rosell J, Carlsson P. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. Eur Urol 2004; 46(6):717-723.

Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366(11):981-990.

Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360(13):1320-1328.

Taylor KL, Shelby R, Gelmann E, McGuire C. Quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. J Natl Cancer Inst 2004; 96(14):1083-1094.

Zhu X, van Leeuwen PJ, Bul M, Bangma CH, Roobol MJ, Schroder FH. Identifying and characterizing "escapes"-men who develop metastases or die from prostate cancer despite screening (ERSPC, section Rotterdam). Int J Cancer 2011; 129(12):2847-2854

Appendix E: Excluded articles – 2024 searches

Article	*PMID/DOI*	*Reason for exclusion*
Alterbeck 2024	https://doi.org/10.1016/j.euf.2022.06.008	Ineligible study design
Arnsrud Godtman R 2015	http://dx.doi.org/10.1016/j.eururo.2014.12.006	Ineligible study design
Arsov 2022	https://doi.org/10.1002/ijc.33940	No outcome metric of interest
Auvinen 2024	https://dx.doi.org/10.1001/jama.2024.3841	No outcome metric of interest
Auvinen 2016	https://doi.org/10.1158/1078-0432.CCR-15-0941	Superseded
Benafif 2022	https://doi.org/:10.1111/bju.15535	Ineligible study design
Bjornebo 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.7131	No outcome metric of interest
Booth 2014	http://dx.doi.org/10.1016/j.eururo.2012.11.041	No outcome metric of interest
Carlsson 2023	https://doi.org/10.1016/j.eururo.2022.10.006	Ineligible analysis
Carlsson 2019	https://doi.org/10.1016/j.eururo.2019.03.010	No population of interest
Clift 2021	https://doi.org/10.3399/bjgp20X713957	Ineligible study design
De Vos 2024	https://doi.org/10.1016/j.eururo.2023.10.011	Ineligible study design
De Vos 2024	https://dx.doi.org/10.1016/S0302-2838%2824%2901236-3	Ineligible publication type
Eldred Evans 2023	https://doi.org/10.1016/j.euo.2023.03.009	Ineligible study design
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	No outcome metric of interest
Garraway 2024	http://doi.org/10.1056/EVIDoa2300289	Ineligible publication type
Godtman 2022	https://doi.org/10.1016/j.eururo.2022.01.018	Ineligible study design
Golijanin 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.029	Ineligible publication type
Hogenhout 2024	https://doi.org/10.1016/j.euo.2023.08.011	Superseded
Hugosson 2022	https://doi.org/10.1056/NEJMoa2209454	No outcome metric of interest
Ilic 2018	http://dx.doi.org/10.1136/bmj.k3519	Superseded
Ilic 2013	https://doi.org/10.1002/14651858.CD004720.pub3	Superseded
John 2024	https://doi.org/10.7196/SAMJ.2024.v114i5.2194	Ineligible publication type
Kilpelainen 2017	http://dx.doi.org/10.1016/j.juro.2017.01.048	No outcome metric of interest
Kim 2023	https://doi.org/10.1016/j.eururo.2022.12.037	Ineligible publication type
Kohestani 2021	https://doi.org/10.1080/21681805.2021.1881612	No outcome metric of interest
Kovac 2020	https://doi.org/10.1001/jamanetworkopen.2019.19284	Ineligible comparator
Krilaviciute 2023	https://doi.org/10.1002/ijc.34295	No outcome metric of interest
Labban 2022	https://doi.org/10.1016/j.eururo.2022.12.028	Ineligible publication type
Landy 2020	https://doi.org/10.1158/1940-6207.CAPR-19-0397	Ineligible study design
Lindberg 2019	https://doi.org/10.1002/ijc.32129	No outcome metric of interest
Liss 2015	http://dx.doi.org/10.1016/j.juro.2014.07.085	No population of interest
Lujan 2014	https//:doi.org/0.1038/pcan.2014.7	Superseded
Lundgren 2018	https://doi.org/10.1016/j.juro.2018.01.080	Ineligible intervention
Martin 2022	https://doi.org/10.1111/bju.15592	Ineligible publication type
Martin 2018	https://doi.org/10.1001/jama.2018.0154	Superseded
Messina 2024	https://doi.org/10.1007/s00330-023-10019-1	No outcome metric of interest

Miller 2018	https://doi.org/10.1002/pros.23540	Ineligible analysis
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	No outcome metric of interest
Nam 2022	https://doi.org/10.1136/bmjopen-2021-059482	No outcome metric of interest
Neupane 2018	https//:doi.org/10.1111/iju.13508	No population of interest
Nevalainen 2024	https://dx.doi.org/10.1136/bmjopen-2023-075595	No outcome metric of interest
Nguyen 2023	https://doi.org/10.1007/s00345-023-04752-x	Ineligible publication type
Nordström 2024	https://doi.org/10.1001/jamanetworkopen.2023.54577	Ineligible study design
Nordström 2021	https://doi.org/10.1016/S1470-2045(21)00348-X	Ineligible study design
Nordström 2019	https://doi.org/10.1136/bmjopen-2018-027816	No outcome metric of interest
Ola 2023	https://doi.org/10.1002/ijc.34274	Ineligible study design
Osses 2019	https://doi.org/10.1016/j.eururo.2018.10.053	No population of interest
Pakarainen 2021	https://doi.org/10.1002/cncr.33254	No outcome metric of interest
Pakarainen 2019	https://doi.org/10.1158/1078-0432.CCR-18-1807	No outcome metric of interest
Paschen 2022	https://doi.org/10.1111/bju.15444	Systematic review with different inclusion criteria
Pinsky 2019	https//:doi.org/10.1177/0969141319839097	Ineligible intervention
Pinsky 2017	https//:doi.org/10.1002/cncr.30474	Superseded
Pinsky 2014	https//:doi.org/10.1111/bju.12368	Ineligible study design
Prorok 2018	https://doi.org/10.2174/1574887113666180409153059	No outcome metric of interest
Ranniko 2022	https://doi.org/10.1111/bju.15683	Ineligible study design
Remmers 2023	https://doi.org/10.1016/j.eururo.2023.03.031	Ineligible study design
Riviere 2024	https://www.auajournals.org/doi/10.1097/JU.0000000000004138	Ineligible study design
Saarimäki 2019	https://doi.org/10.1016/j.euf.2017.07.007	Ineligible study design
Saarimäki 2015	https//:doi.org/10.1002/ijc.29243	Ineligible study design
Schroder 2014	https://doi.org/10.1016/S0140-6736(14)60525-0	Superseded
Segal 2020	https://doi.org/10.1016/j.annonc.2020.06.025	Ineligible study design
Stinesen Kollberg 2022	https://doi.org/10.1097/JU.0000000000002835	No outcome metric of interest
Villers 2020	https://doi.org/10.1016/j.purol.2020.02.011	No outcome metric of interest
Wallström 2022	https://doi.org/10.1016/j.euo.2021.09.001	No population of interest

3.6 Clinical question 6 – PSA testing higher risk males

Clinical question: *For males with no history or symptoms of prostate cancer who are at higher risk of clinically significant prostate cancer or prostate cancer mortality:*

- *At what age should PSA testing commence?*
- *How often should PSA testing occur?*
- *When should PSA testing cease?*
- *What PSA level should be used as a threshold to take further action/investigation?*

Systematic review report: Randomised controlled trials of PSA testing strategies for men at higher risk of clinically significant prostate cancer or prostate cancer mortality

Authors

Suzanne Hughes, Denise Campbell, Susan Yuill, Chelsea Carle, Harriet Hui

PICO

This systematic review addresses the following PICO which is summarised in detail in Table 1.

PICO Question:

For individuals without a prostate cancer diagnosis or symptoms that might indicate prostate cancer who are at higher risk of clinically significant prostate cancer or of prostate cancer mortality what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality, all-cause mortality, or the incidence of metastases at diagnosis or on follow-up?

Table 1. *PICO components*

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Individuals without a prior history of prostate cancer or symptoms that might indicate prostate cancer at higher risk of clinically significant prostate cancer or prostate cancer mortality	A PSA testing strategy with or without digital rectal examination	No PSA testing or another testing strategy	All-cause mortality Prostate cancer-specific mortality Metastatic disease at diagnosis or on follow-up after diagnosis	Randomised controlled trials, pseudo-randomised trials or systematic reviews thereof

1. Methods

1.1 Selection criteria

Table 2. *Selection criteria for systematic review of randomised controlled trials comparing a PSA testing strategy with no PSA testing or another PSA testing strategy for higher risk men*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	Modelling
Study design	Randomised controlled trials, pseudo-randomised trials or systematic reviews thereof	Cohort studies
Population	Individuals with a prostate without a prior history of prostate cancer or symptoms that might indicate prostate cancer at higher or very high risk of clinically significant prostate cancer or prostate cancer mortality e.g. people with a family history of prostate cancer or other BRCA driven cancers (breast and ovarian), germline mutation or African ancestry	Report symptomatic Do not report if symptomatic and restricted to individuals attending tertiary institutions Not restricted to higher risk populations e.g. recruited from a population registry or general population Low SES populations
Intervention	PSA testing strategy with: • or without digital rectal examination • multiple or single/one-off screens • minimum of sextant biopsy	Quadrant biopsy used
Comparator	No PSA testing/opportunistic PSA testing Another testing strategy	
Outcome	Prostate cancer mortality All-cause mortality* Metastatic disease at diagnosis or on follow-up after diagnosis • overall • by age groups	Metastatic disease with follow-up < 4 years**
Publication date	From 1st January 1990 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

SES = socioeconomic status
** Only for trials in which the intervention is testing only for prostate cancer. The PLCO trial intervention is testing for a number of cancers so it is not possible to determine the effects of prostate cancer testing on all-cause survival.*
*** The aim of testing or screening is to detect prostate cancer before it becomes metastatic. Any benefits of screening on the incidence of metastatic disease will not be seen immediately after the baseline screen as the initial screen will detect prevalent metastatic disease. Any benefit i.e. reduction in metastases at diagnosis or overall, will only become apparent after several years of follow-up. In the ERSPC trial a benefit started to be seen 4-5 years after randomisation (Schroder 2012).*

1.2 Definitions and terminology

For the purposes of this review:

Clinically significant prostate cancer refers to ISUP grade ≥ 2 prostate cancer.

Higher or very high risk of clinically significant prostate cancer or prostate cancer mortality refers to at least double the risk of clinically significant prostate cancer or prostate cancer mortality of the general population e.g. brother diagnosed with or died of prostate cancer.

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7 (3+4) or higher on histopathological findings (Epstein 2016).

Metastatic disease refers to M1 disease or a PSA level > 100ng/mL if imaging not available.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website

- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, and meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

For the 2016 guidelines searches were undertaken to identify randomised controlled trials that compared PSA testing with usual care. These searches covered the literature from 1990 up to 2014. The search strategies are documented in Appendices A.1. The full texts identified by these searches for further evaluation were reassessed for inclusion in the current systematic review.

To find evidence published from 2014 onwards the Cochrane Database of Systematic Reviews was searched on 13th March 2024 using the term "prostate", and scoping searches were undertaken to identify recent systematic reviews of randomised controlled trials comparing PSA testing with usual care. Two systematic reviews (Ilic 2018, Paschen 2022) were identified that were considered to cover the relevant literature up to 2019 and consequently, could be used to identify potentially relevant articles up to 2019. To identify potentially relevant articles published from 2019 onwards Medline and Embase databases were searched on 18th March 2024 by combining text words and subject headings for prostate cancer, PSA and screening, together with a filter for randomised controlled trials (RCT/CCT - MEDLINE, Embase search filter. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 2023-11-30). The Cochrane Central Register of Controlled Trials was searched on the 20th March 2024 using a similar search strategy without the filter for randomised controlled trials. These searches were limited to articles published in English from 1st January 2019 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st September 2024. The searches were designed to identify potentially relevant trials in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the searches are included in Appendix A.2. Titles and abstracts were screened by one reviewer. Full texts of potentially relevant articles were retrieved and were assessed independently by two reviewers. Differences were resolved by discussion. Reference lists of recent relevant guidelines and full texts retrieved for further assessment were checked for potential additional articles.

1.5 Data extraction and analyses

Data was extracted from studies that met the selection criteria. One reviewer extracted data from the included studies which was then checked by a second reviewer. The following study characteristics were extracted; country and year of publication, participant number, eligibility and age, setting and enrolment period, intervention components, description or components of comparator arm, relevant outcomes reported, median

follow-up and time frame, subgroup data available, and additional information regarding notable study limitations and possible sources of bias. Effect estimates and their 95% confidence intervals and risks in the control arm were extracted as reported in the study or calculated using relevant reported data. The risks in the intervention arm and the absolute difference between the control and intervention arms were estimated following GRADE guidance outlined in the GRADE Handbook (Schunemann 2013). The magnitude of the absolute difference was determined using thresholds for small, moderate and large absolute effects. These thresholds were determined by a reference group consisting of a consumer, general practitioner and clinical specialist working group members. Where the effect estimate was a hazard ratio the estimated risk in the intervention arm and its confidence interval were calculated using the following formula:

$$1000 \times (1 - S(t)^{HR})$$

where *S(t)* is the estimated probability of no event in the control arm and *HR* is the hazard ratio for the event (Case 2002). Pooled analyses were planned where there were two or more studies reporting the same outcome at corresponding time points.

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias for each of the critical outcomes in each included study using the Cochrane Collaboration Risk of Bias-II tool (Sterne 2019). Disagreements in ratings were resolved by discussion or by a third reviewer. The risk of bias for each outcome for each study was rated low, some concerns or high for the following sources of bias; the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

1.7 GRADE assessment of the certainty of the evidence

GRADE assessments of the certainty of the body of evidence were undertaken for each critical outcome (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence). For this systematic review prostate cancer mortality was considered a critical outcome.

The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Schunemann 2013) and Schunemann et al 2022 and on guidance for assessing narrative syntheses provided by Murad 2017. For the assessment of risk of bias, contamination i.e. PSA testing in the absence of symptoms, in the control group was considered the most important potential source of bias likely distorting effect estimates towards the null. Imprecision was assessed in the context of whether there was a clinically important decrease rather than the magnitude of the decrease, using thresholds for a minimal clinically important difference (MCID) or small absolute difference. These thresholds were determined by a reference group consisting of a consumer, a general practitioner, a urology nurse practitioner and clinical specialists following GRADE guidance provided by Schunemann 2022. Potential publication bias (or small study effects) was assessed using a Funnel Plot if 10 or more studies. Where there were less than 10 studies, clinical trial registries were searched for potentially relevant trials (see Section 1.8 below for search details) that had planned completion dates prior to 2020 (5 or more years ago), that had not been terminated and for which results had not been published suggesting publication bias. We assessed the certainty of the evidence

as to whether to offer PSA testing as well as the certainty of the evidence as to which PSA testing protocol to use.

As per GRADE guidance, randomised controlled trials started with a high level of certainty in the evidence and were to be downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

Definitions of the GRADE ratings of certainty of the overall body of evidence are presented in Appendix B.

1.8 Clinical trial registry searches

Potentially relevant ongoing and unpublished trials were identified from literature searches, recent guidelines and by clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 20th March 2025.

The clinical trial registries were searched with the search terms listed below:

Clinicaltrials.gov using the terms:

"prostate cancer" and "screening"

"prostate cancer" and "detection/screening"

"prostate cancer" and "test"

"prostate cancer" and "PSA"

International Clinical Trials Registry Platform using the terms:

"prostate cancer" and "screening"

"prostate cancer" and "detection"

"prostate cancer" and "test"

"prostate cancer" and "PSA"

Australia and New Zealand Clinical Trial Registry using the terms:

"prostate cancer" and "early detection/screening" or "diagnosis/prognosis"

"prostate cancer" and "screening"

"prostate cancer" and "detection"

"prostate cancer" and "test"

"prostate cancer" and "PSA"

2. Results

2.1 Guidelines searches

Four potentially relevant guidelines were identified which were reportedly based on systematic reviews of the literature published from 2014 onwards. They were not considered for adoption; for all four guidelines the systematic reviews of the evidence were not accessible, and for three of the guidelines risk of bias and GRADE assessments were not mentioned in the reported systematic review methods. (Appendix C).

2.2 Literature searches

Figure 1 outlines the process for identifying relevant articles published from 1990 onwards. An appraisal of the 33 full texts considered for the 2016 guidelines did not identify any relevant articles for inclusion. For the literature searches for the 2025 guidelines update, eighteen potentially relevant articles were identified from the Ilic 2018 and Paschen 2022 systematic reviews. The Medline, Embase and CENTRAL database searches retrieved 158 unique citations which were assessed by one reviewer of which 52 articles were retrieved for a more detailed evaluation by two reviewers. Five articles were identified for full text evaluation from scoping searches or from reference lists of recent relevant guidelines and full texts retrieved for further assessment. One randomised controlled trial met the inclusion criteria. There were no studies that included Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.

The retrieved articles that were not included in this review and the reasons for their exclusion are documented in Appendices D and E. The main reason for exclusion was no population of interest.

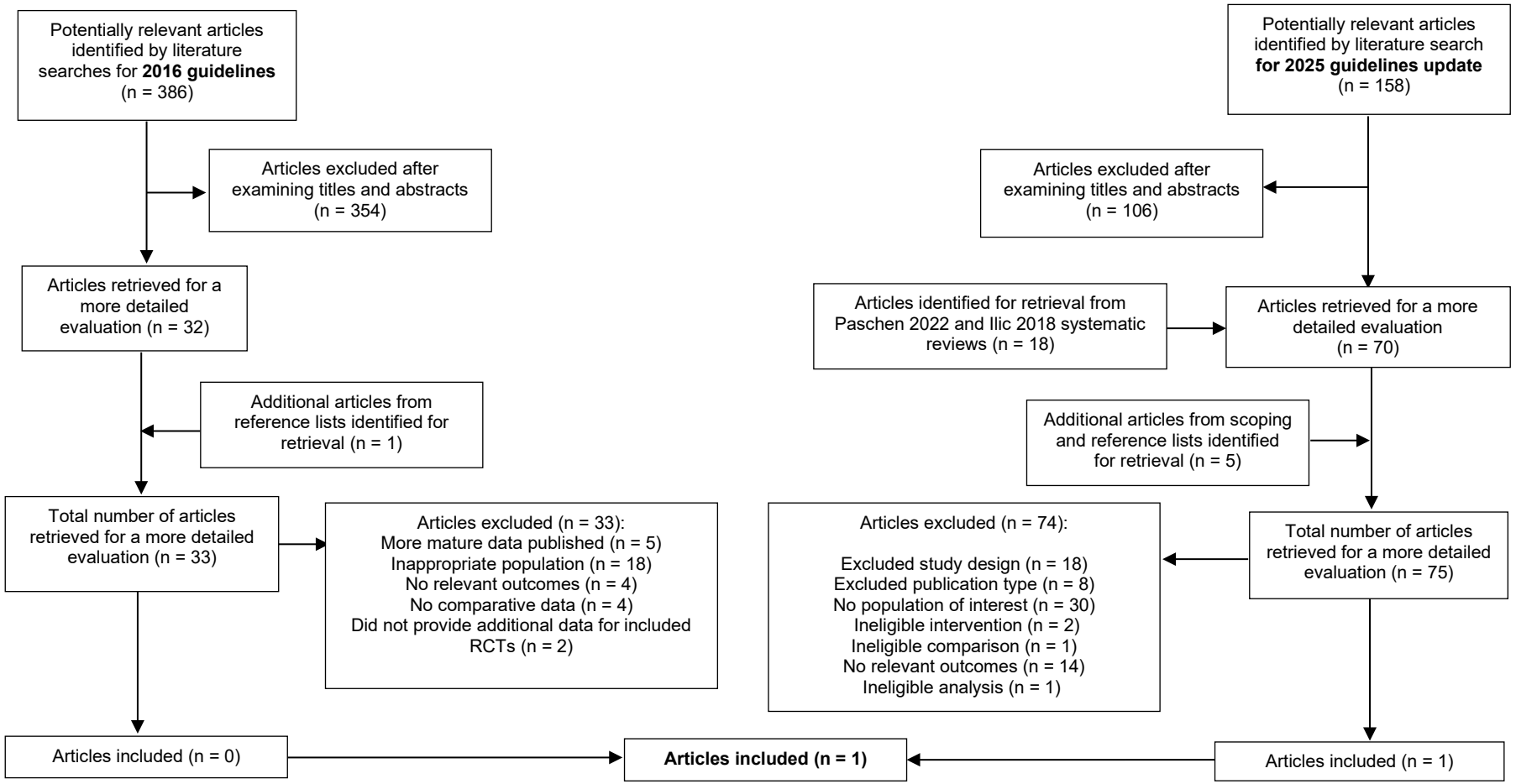

Figure 1. *Process of inclusion and exclusion of published articles*

2.3 Study Characteristics

Characteristics of the included studies are described in Table 3.

Table 3. *Characteristics of randomised controlled trials comparing PSA testing strategies ± DRE compared to no PSA testing reporting outcomes of prostate cancer-specific mortality, overall mortality and/or incidence of metastases at diagnosis or on follow-up for individuals at high-risk of prostate cancer*

Study	*Setting and enrolment period*	*Participants*	*Intervention*	*Comparator*	*Relevant Outcomes*	*Comments*
Liss 2015 (USA) Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) NCT00002540	10 tertiary centres 1993-2001	Men aged 55-74 years Exclusions: Included personal history of prostate, lung or colorectal cancer, used finasteride in last 6 months or currently receiving cancer treatment From April 1995, men reporting more than one PSA test in the previous 3 years also excluded *White subgroup:* N = 65,179 Median follow-up: 11.6 years ***Sub-analysis*** White men who reported a **family history** at baseline (immediate family member) of **prostate cancer** **N = 4833** Median age: 62 years 100% white	Annual PSA testing for 6 years PSA threshold > 4.0ng/mL Plus Annual DRE for the first 4 years White men who reported a baseline **family history** N = 2483 % who underwent testing: NR % test positive who underwent biopsy: NR	Usual care (included opportunistic screening) White men who reported a baseline **family history** N = 2350 % who had a PSA test: NR	**Prostate cancer-specific mortality** ascertained through periodic linkage to the National Death Index, review of death certificates and panel review of data to determine cause of death. The underlying cause of death was determined in a uniform and unbiased manner from the death certificate and relevant medical records	Small number of events (27 deaths in 4833 men with a family history of prostate cancer) In the entire PLCO cohort • Based on surveys 46% contamination (tests as part of routine health check-up in previous year) in control arm • 84% received screening test each year of screening in screening arm • 32% and 22% underwent biopsy following positive PSA test and DRE respectively in screening arm All participants provided written informed consent

DRE = digital rectal examination; N = number; NR = not reported; PSA = prostate-specific antigen

2.4 Results by outcomes of interest

Prostate cancer mortality: One randomised controlled trial identified – Results reported in Table 4

Overall mortality: No randomised controlled trials identified

Metastatic disease: No randomised controlled trials identified

Table 4. *Results of randomised controlled trials comparing PSA testing strategies ± DRE compared to no PSA testing for the outcome of prostate cancer-specific mortality for individuals at high risk of prostate cancer*

Study	*N*	*Median follow-up*	*Time frame*	*Age at enrolment*	*Risk in control arm per 10,000*	*Effect estimate (95%CI)*	*Estimated risk in intervention arm (95%CI) per 10,000*	*Absolute difference (95% CI) per 10,000*
PSA testing protocol = annual PSA test using threshold of 4 ng/mL for 6 years + annual DRE for 4 years								
Liss 2015 (PLCO)	4833	NR 11.6 years (maximum 13.3 years) for entire white cohort	For subgroup with family history 11 years	55-74 years	~62*	HR = 0.49 (0.22-1.10)	30.4 (13.7-68.2)	32 fewer (48 fewer to 6 more)
			13 years	55-74 years	~86*	HR = 0.49 (0.22-1.10)	42.1 (18.9-94.6)	44 fewer (67 fewer to 9 more)
			13 years	55-74 years	76.6	HR = 0.49 (0.22-1.10)	37.6 (16.9-84.3)	39 fewer (60 fewer to 8 more)

CI = confidence interval; DRE = digital rectal examination; HR = hazard ratio; N = number; NR = not reported; PSA = prostate-specific antigen; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

** Cumulative probability estimated by technical team from Figure 1*

2.5 Risk of bias

The results of the risk of bias assessments for the included studies are shown in Table 5.

Table 5. *Risk of bias assessments for included studies of randomised controlled trials using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) (Sterne 2019)*

Outcome	*Study*	*Source of bias*					*Overall risk of bias*
		Randomisation process	*Deviations from intended interventions*	*Missing outcome data*	*Measurement of the outcome*	*Selection of the reported result*	
Prostate cancer-specific mortality	Liss 2015 (PLCO)	Some concerns	High	Low	Low	Some concerns	High

PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
Key to overall rating
Low risk of bias: "Low" for all domains
Some concerns regarding risk of bias: "Some concerns" but not "high" for one or more domains
High risk of bias: "High" for one or more domains

3. GRADE assessments of the certainty of the evidence

Prostate cancer mortality – GRADE assessments of the certainty of the evidence are shown in Table 6

Table 6. *GRADE assessment of the certainty of the evidence for prostate cancer mortality from randomised controlled trials comparing a PSA testing protocol with usual care in a higher risk population.*

GRADE domain	Rating	Reason for rating	Certainty of evidence
Annual PSA testing using threshold of 4 ng/mL for 6 years + annual DRE for 4 years starting at age 55-74 years			
Risk of bias	*Whether to test* No serious concerns *Protocol* Serious concerns	For the single trial reporting this outcome, a subgroup of the PLCO trial, the risk of bias due to deviations from intended interventions was considered high with 46% of those in the usual care arm of the main trial receiving a PSA test as part of routine health check-up in the past year likely leading to the underestimation of the effects of the intervention. As PSA testing resulted in a clinically significant moderate decrease in prostate cancer mortality despite high levels of contamination, contamination was not considered a major source of bias when considering the certainty of the evidence regarding whether to offer PSA testing to higher risk men.	***Whether to test*** ***MODERATE*** ***Protocol*** ***VERY LOW***
Indirectness	*Whether to test* No serious concerns *Protocol* Serious concerns	Approximately 50% of participants in the main trial had received a PSA test in the 3 years prior to enrolment. In addition, participants were recruited by 10 tertiary care institutions rather than from the general population. Consequently, the results may not be directly relevant to an unscreened population at higher risk of prostate cancer mortality or clinically significant prostate cancer in the primary care setting. As PSA testing resulted in a clinically significant moderate decrease in prostate cancer mortality despite high baseline levels of PSA testing, indirectness was not considered a serious concern when considering the certainty of the evidence regarding whether to offer PSA testing to higher risk men.	
Imprecision	*Whether to test* Serious concerns *Protocol* Very serious concerns	Based on a hazard ratio at 11 years of 0.49 with a 95% confidence interval of 0.22 to 1.10, in a population of 10,000 men annual PSA testing for 6 years using a threshold of 4 ng/mL starting at ages 55-74 years plus an annual DRE for the first 4 years is estimated to result in 32 fewer (48 fewer to 6 more) prostate cancer deaths when compared with usual care. Using a MCID of 11 prostate cancer deaths per 10,000 men and thresholds for moderate and large effects of 22 prostate cancer deaths per 10,000 and 44 prostate cancer deaths per 10,000, the absolute difference between the two arms was a clinically important, moderate decrease however the 95%CI crossed two thresholds and included clinically unimportant changes in prostate cancer deaths. When considering the certainty of the evidence regarding whether to offer PSA testing to higher risk men imprecision was assessed in the context as to whether the decrease in prostate cancer mortality was clinically significant, whereas when considering the certainty of the evidence regarding which protocol to use imprecision was assessed in the context as to the certainty of the magnitude of the effect.	
Inconsistency	Not Assessable	Not assessable as only a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had had planned completion dates prior to 2020 that had not been terminated early.	

CI = confidence interval; DRE = digital rectal examination; MCID = minimal clinically important difference; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA = prostate specific antigen

4. Summary of findings

Table 7. *Summary of findings for randomised controlled trials comparing a PSA testing protocol with usual care in a higher risk population*

Outcome (MCID)	Time frame	RCTs (N)	Participants (N)	Study results and measurements	Absolute effect estimates per 10,1000				Certainty of evidence (GRADE)	Plain text summary
					Metric	Usual care	PSA testing (95% CI)	Absolute difference (95% CI)		
Annual PSA testing using threshold of 4 ng/mL for 6 years + annual DRE for 4 years starting at age 55-74 years vs usual care										
Prostate cancer mortality (11/10,000)	11 years	1	4833	HR: 0.49 (95%CI: 0.22, 1.10)	Prostate cancer deaths per 10,000	62	30.4 (13.7-68.2)	32 fewer (48 fewer to 6 more)	***Whether to screen*** Moderate[1]	In a population of asymptomatic men at higher risk of prostate cancer mortality or clinically significant disease PSA testing likely results in a clinically **important** (moderate)^ reduction in prostate cancer mortality at 11 years when compared with usual care.
									Protocol Very low[2]	In a population of asymptomatic men at higher risk of prostate cancer mortality or clinically significant disease we are uncertain as to whether annual PSA testing using a threshold of 4 ng/mL for 6 years starting at ages 55 to 74 plus annual DRE for the first 4 years results in a clinically **important** (moderate)^ reduction in prostate cancer mortality at 11 years when compared with usual care.

CI = confidence interval; DRE = digital rectal examination; HR = hazard ratio; N = number; MCID = minimally important difference; RCT = randomised controlled trial

[1] *Downgraded by one level due to serious concerns re imprecision*

[2] *Downgraded by three levels due to very serious concerns re imprecision, and serious concerns re risk of bias and indirectness*

^ *Using thresholds of 11, 22 and 44 prostate cancer deaths per 10,000 men at 11 years for small (minimal clinically important difference), moderate and large effects*

5. Ongoing clinical trials

One potentially relevant ongoing trial was identified from literature searches, clinical trial registry searches or from recent guidelines, and is described in Table 8.

Table 8. *Summary of potentially relevant ongoing randomised controlled trials comparing a PSA testing protocol with usual care in a higher risk population*

Study ID	Study name, location and study design	Start date	Planned completion date	Status	Population	Intervention	Comparator	Outcomes
ISRCTN37591328	PROBASE Germany RCT – 2 arms	2014	2034?	Active, not recruiting	Men aged 45 years	Immediate PSA-stratified PSA screening	Immediate offer of DRE only PSA-stratified PSA screening starting at age 50	Prostate cancer detection *At age 60* • Metastases • Metastases after treatment • Prostate cancer mortality • Overall survival

DRE = digital rectal examination; PSA = prostate-specific antigen; RCT = randomised controlled trial

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APPENDICES

Appendix A: Literature search strategies

A.1 Search strategies used for the 2016 guidelines

Database: Medline

#	*Search terms*
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	prostate-specific antigen/
5	prostate specific antigen.tw,mp.
6	PSA.mp,tw.
7	4 or 5 or 6
8	exp mass screening/
9	"early detection of cancer"/
10	screen$.mp,tw.
11	8 or 9 or 10
12	clinical trial.pt.
13	random$.mp.
14	((single or double) adj3 (blind$ or mask$)).mp,tw.
15	placebo$.mp,tw.
16	12 or 13 or 14 or 15
17	3 and 7 and 11 and 16
18	limit 17 to (english language and humans and yr="2012-current")

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b). Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report. Canberra: National Health and Medical Research Council.

Aboriginal and Torres Strait Island related search terms used

#	*Search terms*
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

Database: Embase

#	*Search terms*
1	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neopla* OR metast* OR adeno*)
2	'prostate cancer'/exp
3	1 OR 2
4	'prostate specific antigen'/exp
5	'prostate specific antigen':de,ab,ti OR psa:de,ab,ti
6	'prostate specific antigen' OR psa
7	4 OR 5 OR 6
8	'mass screening'/exp
9	'screening test'/exp
10	'early diagnosis'/exp
11	screen*
12	8 OR 9 OR 10 OR 11

13	'clinical trial'
14	'clinical trial':de
15	random*
16	random*:ab,ti
17	(single OR double) NEAR/3 (blind* OR mask*)
18	((single OR double) NEAR/3 (blind* OR mask*)):ab,ti
19	placebo*
20	placebo:ab,ti
21	13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22	[embase]/lim AND [2012-2014]/py AND [english]/lim AND [humans]/lim
23	3 AND 7 AND 12 AND 21 AND 22

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b). Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report. Canberra: National Health and Medical Research Council.

Aboriginal and Torres Strait Island related search terms used

#	***Search terms***
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

Database: CENTRAL

#	***Search terms***
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	Prostate-Specific Antigen/
5	prostate specific antigen.tw,mp.
6	psa.tw,mp.
7	4 or 5 or 6
8	exp mass screening/
9	"early detection of cancer"/
10	screen$.mp,tw.
11	8 or 9 or 10
12	clinical trial.pt.
13	random$.mp.
14	((single or double) adj3 (blind$ or mask$)).mp,tw.
15	placebo$.mp,tw.
16	12 or 13 or 14 or 15
17	3 and 7 and 11 and 16
18	limit 17 to (yr="2012-current")

Modification of search strategies used by Ilic et al 2013. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD004720 and National Health and Medical Research Council (2013b).
For Cochrane Database of Systematic Reviews – The Cochrane Library: Title, abstracts, keywords: “prostate”

Database: Abstracts of Reviews of Effects and Health Technology Assessment database (via OvidSP)

#	*Search terms*
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	1 or 2

A.2 Search strategies used to identify articles published 2019 onwards

Databases: Medline and Embase database (via Ovid platform)

#	*Search terms*
1	exp Prostatic Neoplasms/
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).tw.
3	1 or 2
4	exp prostate-specific antigen/
5	prostate specific antigen.tw.
6	PSA.tw.
7	4 or 5 or 6
8	exp mass screening/
9	exp “early detection of cancer”/
10	8 or 9
11	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
12	Randomized Controlled Trial/
13	exp Randomized Controlled Trials as Topic/
14	“Randomized Controlled Trial (topic)”/
15	Controlled Clinical Trial/
16	exp Controlled Clinical Trials as Topic/
17	“Controlled Clinical Trial (topic)”/
18	Randomization/
19	Random Allocation/
20	Double-Blind Method/
21	Double Blind Procedure/
22	Double-Blind Studies/
23	Single-Blind Method/
24	Single Blind Procedure/
25	Single-Blind Studies/
26	Placebos/
27	Placebo/
28	Control Groups/
29	Control Group/
30	(random* or sham or placebo*).ti,ab,hw,kf.
31	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
32	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
33	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
34	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
35	allocated.ti,ab,hw.
36	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.

37	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
38	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
39	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
40	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
41	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
42	or/11-41
43	3 and 7 and 10 and 42
44	limit 43 to (english language and humans and yr="2019-current")

Includes RCT / CCT - MEDLINE, Embase search filter. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 30/11/2023.

Database: Cochrane Central Register of Controlled Trials

#	***Search terms***
1	*exp Prostatic Neoplasms/*
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).tw.
3	1 or 2
4	exp prostate-specific antigen/
5	prostate specific antigen.tw.
6	PSA.tw.
7	4 or 5 or 6
8	exp mass screening/
9	exp "early detection of cancer"/
10	8 or 9
11	3 and 7 and 10
12	limit 11 to (english language and humans and yr="2019-current")

Appendix B: GRADE assessment of the certainty of the evidence

Grade	***Definition***
⊕⊕⊕⊕ High certainty	We are very confident that the true effect lies close to that of the estimate of the effect.
⊕⊕⊕◯ Moderate certainty	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ Low certainty	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
⊕◯◯◯ Very low certainty	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reportedly based on systematic reviews

Developer	***Publication or link***	***Title***	***Year***	***Reasons for not adopting***
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Systematic reviews of the evidence were not accessible. No relevant evidence reported
British Columbia	https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines	Prostate Cancer Part 1: Diagnosis and Referral in Primary Care	2020	Systematic reviews of the evidence were not accessible and the reported systematic review methods did not mention

				risk of bias or GRADE assessments or the evidence to decision processes used. State found no evidence for testing protocols for high-risk men
Canadian Urological Association	http://dx.doi.org/10.5489/cuaj.7851	UPDATE – 2022 Canadian Urological Association recommendations on prostate cancer screening and early diagnosis	2022	Systematic reviews of the evidence were not accessible and the reported systematic review methods did not mention risk of bias or GRADE assessments or the evidence to decision processes used.
Prostate Cancer Foundation (USA)	Garroway et al. 2024 https://www.doi.org/10.1056/EVIDoa2300289	Prostate Cancer Foundation Screening Guidelines for Black Men in the United States	2024	Systematic reviews of the evidence were not accessible and the reported systematic review methods did not mention risk of bias or GRADE assessments.

Appendix D: Excluded articles - 2016 guidelines searches

Article	*Reason for exclusion*
Andriole 2012	No population of interest
Andriole 2009	No population of interest
Andriole 2005	No comparative data
Aus 2007	More mature data published
Bokhorst 2014	No population of interest
Carlsson 2011	No population of interest
Crawford 2011	More mature data published
Djulbegovic 2010	No population of interest
Grenabo Bergdahl 2013	No population of interest
Grenabo Bergdahl 2009	No comparative data
Hugosson 2010	No population of interest
Ilic 2013	No population of interest
Johnson 2006	No relevant outcomes
Kerkhof 2010	More mature data published
Kilpelainen 2013	No population of interest
Kilpelainen 2011	No relevant outcomes
Kilpelainen 2010	No relevant outcomes
Kjellman 2009	No population of interest
Labrie 2004	No population of interest
Lin 2011	Did not provide original or additional data for RCTs included for Q4.1
Lumen 2012	No population of interest
New Zealand Guidelines Group 2009	Did not provide original or additional data for RCTs included for Q4.1
Pinsky 2012	No population of interest
Raaijmakers 2002	No comparative data
Roobol 2013	No population of interest
Roobol 2009	More mature data published
Sandblom 2011	No population of interest
Sandblom 2004	No population of interest
Schroder 2012	No population of interest
Schroder 2012	No population of interest
Schroder 2009	More mature data published
Taylor 2004	No relevant outcomes
Zhu 2011	No comparative data

References of excluded articles – 2016 guidelines

Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104(2):125-132.

Andriole GL, Crawford ED, Grubb RL, III, Buys SS, Chia D, Church TR et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360(13):1310-1319.

Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, Chia D et al. Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. J Natl Cancer Inst 2005; 97(6):433-438.

Aus G, Bergdahl S, Lodding P, Lilja H, Hugosson J. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer--results from a prospective, population-based randomized controlled trial. Eur Urol 2007; 51(3):659-664.

Bokhorst LP, Bangma CH, van Leenders GJ, Lous JJ, Moss SM, Schroder FH et al. Prostate-specific antigen-based prostate cancer screening: reduction of prostate cancer mortality after correction for nonattendance and contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2014; 65(2):329-336.

Carlsson SV, Holmberg E, Moss SM, Roobol MJ, Schroder FH, Tammela TL et al. No excess mortality after prostate biopsy: results from the European Randomized Study of Screening for Prostate Cancer. BJU Int 2011; 107(12):1912-1917.

Crawford DE, Grubb R, Black A, Andriole GL, Chen M-H, Izmirlian G et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. J Clin Oncol 2011; 29(4): 355-361.

Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, Djulbegovic B et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ 2010; 341:c4543.

Grenabo Bergdahl A, Holmberg E, Moss S, Hugosson J. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. Eur Urol 2013; 64(5):703-709.

Grenabo Bergdahl A, Aus G, Lilja H, Hugosson J. Risk of dying from prostate cancer in men randomized to screening: differences between attendees and nonattendees. Cancer 2009; 115(24):5672-5679.

Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010; 11(8):725-732.

Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013; 1:CD004720.

Johnson DB. The effects of an abnormal cancer screening test on health related quality of life. International Journal of Cancer Research 2006; 2(3):277-289.

Kerkhof M, Roobol MJ, Cuzick J, Sasieni P, Roemeling S, Schroder FH et al. Effect of the correction for noncompliance and contamination on the estimated reduction of metastatic prostate cancer within a randomized screening trial (ERSPC section Rotterdam). Int J Cancer 2010; 127(11):2639-2644.

Kilpelainen TP, Tammela TL, Malila N, Hakama M, Santti H, Maattanen L et al. Prostate cancer mortality in the Finnish randomized screening trial. Journal of the National Cancer Institute 2013; 105(10):719-725.

Kilpelainen TP, Tammela TL, Roobol M, Hugosson J, Ciatto S, Nelen V et al. False-positive screening results in the European randomized study of screening for prostate cancer. Eur J Cancer 2011; 47(18):2698-2705.

Kilpelainen TP, Tammela TL, Maattanen L, Kujala P, Stenman UH, Ala-Opas M et al. False-positive screening results in the Finnish prostate cancer screening trial. Br J Cancer 2010; 102(3):469-474.

Kjellman A, Akre O, Norming U, Tornblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. J Urol 2009; 181(4):1615-1621.

Labrie F, Candas B, Cusan L, Gomez JL, Belanger A, Brousseau G et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate 2004; 59(3):311-318.

Lin K, Croswell JM, Koenig H, Lam C, Maltz A. Prostate-specific antigen-based screening for prostate cancer: an evidence update for the U.S. preventive services task force. Evidence synthesis no.90. 2011. Rockville, MD, Agency for Healthcare Research and Quality.

Lumen N, Fonteyne V, De MG, Ost P, Villeirs G, Mottrie A et al. Population screening for prostate cancer: an overview of available studies and meta-analysis. Int J Urol 2012; 19(2):100-108.

New Zealand Guidelines Group. Cancer control strategy guidance completion: update of evidence for prostate-specific antigen (PSA) testing in asymptomatic men. 2009. Wellington, Ministry of Health.

Pinsky PF, Black A, Parnes HL, Grubb R, David CE, Miller A et al. Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiol 2012; 36(6):e401-e406.

Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schroder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002; 60(5):826-830.

Roobol MJ, Kranse R, Bangma CH, Van Leenders AGJL, Blijenberg BG, Van Schaik RHN et al. Screening for prostate cancer: Results of the Rotterdam section of the European randomized study of screening for prostate cancer. Eur Urol 2013; 64(4):530-539.

Roobol MJ, Kerkhof M, Schroder FH, Cuzick J, Sasieni P, Hakama M et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2009; 56(4):584-591.

Sandblom G, Varenhorst E, Rosell J, Lofman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. BMJ 2011; 342:d1539.

Sandblom G, Varenhorst E, Lofman O, Rosell J, Carlsson P. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. Eur Urol 2004; 46(6):717-723.
Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366(11):981-990.

Schroder FH, Hugosson J, Carlsson S, Tammela T, Maattanen L, Auvinen A et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012; 62(5):745-752.

Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360(13):1320-1328.

Taylor KL, Shelby R, Gelmann E, McGuire C. Quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. J Natl Cancer Inst 2004; 96(14):1083-1094.

Zhu X, van Leeuwen PJ, Bul M, Bangma CH, Roobol MJ, Schroder FH. Identifying and characterizing "escapes"-men who develop metastases or die from prostate cancer despite screening (ERSPC, section Rotterdam). Int J Cancer 2011; 129(12):2847-2854.

Appendix E: Excluded articles – 2025 guidelines

Article	*PMID/DOI*	*Reason for exclusion*
Alterbeck 2024	https://doi.org/10.1016/j.euf.2022.06.008	Ineligible study design
Arnsrud Godtman R 2015	http://dx.doi.org/10.1016/j.eururo.2014.12.006	Ineligible study design
Arsov 2022	https://doi.org/10.1002/ijc.33940	No outcome metric of interest
Auvinen 2024	https://dx.doi.org/10.1001/jama.2024.3841	No outcome metric of interest
Auvinen 2016	https://doi.org/10.1158/1078-0432.CCR-15-0941	No population of interest
Bancroft 2024	https://doi.org/10.1111/bju.16432	Ineligible study design
Benafif 2022	https://doi.org/:10.1111/bju.15535	Ineligible study design
Bjornebo 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.7131	No outcome metric of interest
Booth 2014	http://dx.doi.org/10.1016/j.eururo.2012.11.041	No outcome metric of interest
Buzzoni 2015	https://doi.org/10.1016/j.eururo.2015.02.042.	No population of interest
Carlsson 2023	https://doi.org/10.1016/j.eururo.2022.10.006	No population of interest
Carlsson 2019	https://doi.org/10.1016/j.eururo.2019.03.010	No population of interest
Clift 2021	https://doi.org/10.3399/bjgp20X713957	No population of interest
De Vos 2024	https://doi.org/10.1016/j.eururo.2023.10.011	Ineligible study design
De Vos 2024	https://dx.doi.org/10.1016/S0302-2838%2824%2901236-3	Ineligible publication type
De Vos 2023	https://doi.org/10.1016/j.eururo.2023.03.016	No population of interest
Eldred Evans 2023	https://doi.org/10.1016/j.euo.2023.03.009	Ineligible study design
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	No outcome metric of interest
Frånlund 2022	https://doi.org/10.1097/JU.0000000000002696	No population of interest
Garraway 2024	http://doi.org/10.1056/EVIDoa2300289	Ineligible publication type
Godtman 2022	https://doi.org/10.1016/j.eururo.2022.01.018	Ineligible study design
Golijanin 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.029	Ineligible publication type
Hogenhout 2024	https://doi.org/10.1016/j.euo.2023.08.011	No population of interest
Hugosson 2022	https://doi.org/10.1056/NEJMoa2209454	No outcome metric of interest

Hugosson 2019	https://doi.org/10.1016/j.eururo.2019.02.009	No population of interest
Hugosson 2018	https//:doi.org/10.1080/21681805.2017.1411392	No population of interest
Ilic 2018	http://dx.doi.org/10.1136/bmj.k3519	No population of interest
Ilic 2013	https://doi.org/10.1002/14651858.CD004720.pub3	No population of interest
John 2024	https://doi.org/10.7196/SAMJ.2024.v114i5.2194	Ineligible publication type
Kilpelainen 2017	http://dx.doi.org/10.1016/j.juro.2017.01.048	No population of interest
Kim 2023	https://doi.org/10.1016/j.eururo.2022.12.037	Ineligible publication type
Kohestani 2021	https://doi.org/10.1080/21681805.2021.1881612	No outcome metric of interest
Kovac 2020	https://doi.org/10.1001/jamanetworkopen.2019.19284	Ineligible comparator
Krilaviciute 2023	https://doi.org/10.1002/ijc.34295	No outcome metric of interest
Labban 2022	https://doi.org/10.1016/j.eururo.2022.12.028	Ineligible publication type
Landy 2020	https://doi.org/10.1158/1940-6207.CAPR-19-0397	Ineligible study design
Lindberg 2019	https://doi.org/10.1002/ijc.32129	No population of interest
Lujan 2020	https://doi.org/10.1016/j.acuro.2020.01.005	No population of interest
Lujan 2014	https//:doi.org/0.1038/pcan.2014.7	No population of interest
Lundgren 2018	https://doi.org/10.1016/j.juro.2018.01.080	No population of interest
Martin 2024	http://doi.org/0.1001/jama.2024.4011	No population of interest
Martin 2022	https://doi.org/10.1111/bju.15592	Ineligible publication type
Martin 2018	https://doi.org/10.1001/jama.2018.0154	No population of interest
Messina 2024	https://doi.org/10.1007/s00330-023-10019-1	No outcome metric of interest
Miller 2018	https://doi.org/10.1002/pros.23540	Ineligible analysis
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	No outcome metric of interest
Nam 2022	https://doi.org/10.1136/bmjopen-2021-059482	No outcome metric of interest
Neupane 2018	https//:doi.org/10.1111/iju.13508	No population of interest
Nevalainen 2024	https://dx.doi.org/10.1136/bmjopen-2023-075595	No outcome metric of interest
Nguyen 2023	https://doi.org/10.1007/s00345-023-04752-x	Ineligible publication type
Nordström 2024	https://doi.org/10.1001/jamanetworkopen.2023.54577	Ineligible study design
Nordström 2021	https://doi.org/10.1016/S1470-2045(21)00348-X	Ineligible study design
Nordström 2019	https://doi.org/10.1136/bmjopen-2018-027816	No outcome metric of interest
Ola 2023	https://doi.org/10.1002/ijc.34274	Ineligible study design
Osses 2019	https://doi.org/10.1016/j.eururo.2018.10.053	No population of interest
Pakarainen 2021	https://doi.org/10.1002/cncr.33254	No outcome metric of interest
Pakarainen 2019	https://doi.org/10.1158/1078-0432.CCR-18-1807	No population of interest
Paschen 2022	https://doi.org/10.1111/bju.15444	No population of interest
Pinsky 2019	https://doi.org/10.1111/bju.14580	No population of interest
Pinsky 2019	https://doi.org/10.1002/cncr.32176	No population of interest
Pinsky 2019	https//:doi.org/10.1177/0969141319839097	Ineligible intervention
Pinsky 2017	https//:doi.org/10.1002/cncr.30474	No population of interest
Pinsky 2014	https//:doi.org/10.1111/bju.12368	Ineligible study design
Prorok 2018	https://doi.org/10.2174/1574887113666180409153059	No population of interest
Ranniko 2022	https://doi.org/10.1111/bju.15683	Ineligible study design
Remmers 2023	https://doi.org/10.1016/j.eururo.2023.03.031	Ineligible study design
Riviere 2024	https://www.auajournals.org/doi/10.1097/JU.0000000000004138	Ineligible study design
Saarimäki 2019	https://doi.org/10.1016/j.euf.2017.07.007	Ineligible study design

Saarimäki 2015	https//:doi.org/10.1002/ijc.29243	Ineligible study design
Schroder 2014	https://doi.org/10.1016/S0140-6736(14)60525-0	No population of interest
Segal 2020	https://doi.org/10.1016/j.annonc.2020.06.025	Ineligible study design
Stinesen Kollberg 2022	https://doi.org/10.1097/JU.0000000000002835	No population of interest
Villers 2020	https://doi.org/10.1016/j.purol.2020.02.011	No population of interest
Wallström 2022	https://doi.org/10.1016/j.euo.2021.09.001	No population of interest

3.7 Clinical question 7 – mpMRI PICO 7A

Clinical question: *Can/should we use mpMRI to triage men with no history of prostate cancer and an elevated PSA for biopsy?*

Systematic review report for PICO 7A: Diagnostic accuracy of multiparametric MRI in biopsy naïve men for the diagnosis of clinically significant prostate cancer

Authors

Chelsea Carle, Isabel Rewais, Susan Yuill, Michael David, Suzanne Hughes

PICO 7A

This systematic review addresses the following PICO which is summarised in detail in Table 1.

For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, how does mpMRI triage for biopsy compare with all individuals undergoing biopsy for diagnostic accuracy outcomes?

Table 9. *PICO components*

Study design	*Population*	*Index test*	*Reference Standard*	*Outcomes#*
Cross-sectional diagnostic accuracy studies, or systematic reviews thereof	Individuals with no history of prostate cancer with elevated PSA levels undergoing initial prostate biopsy (biopsy naïve)	mpMRI PIRADS/Likert ≥ 3 or mpMRI PIRADS/Likert ≥ 4	Systematic or template biopsy ≥ 20 cores +/- targeted biopsies	Diagnostic performance (sensitivity and specificity) related to: ISUP grade ≥ 2 prostate cancer ISUP grade 1 prostate cancer ISUP grade ≥ 3 prostate cancer

Overall, or by age, PSA level or risk

1. Methods

1.1 Selection Criteria

Table 10. *Selection criteria for systematic review of the diagnostic accuracy of multiparametric MRI in biopsy naïve men for the diagnosis of clinically significant prostate cancer*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Diagnostic accuracy	
Study design	Cross-sectional head-to-head studies, or systematic reviews thereof	Diagnostic case-control studies or studies of diagnostic yield.
Population	Individuals with a clinical suspicion of prostate cancer due to elevated PSA levels or abnormal DRE undergoing initial prostate biopsy (biopsy naïve) including age, PSA level or risk level restricted subgroups	Clinical suspicion based on positive DRE only (not based on PSA test). Patients had prior biopsy (negative or positive) Individuals with prior prostate cancer diagnosis. > 10% of population have undergone prior biopsy and outcomes not for stratified for biopsy-naïve patients.
Index test	mpMRI (T2-weighted imaging + DWI + DCE) prior to biopsy and a score ≥3, or ≥4 on PIRADS v1, v2 or v2.1 or 5-point Likert scale	Biparametric mpMRI (no DCE). mpMRI includes MRS and results not available for mpMRI alone. Not 5-point Likert scale. mpMRI threshold unclear or not reported.
Reference standard	≥ 20 core systematic (includes template and saturation biopsies) biopsy* regardless of index test results +/- mpMRI-targeted biopsy^ if targeted biopsies undertaken **Study must include and report results for both mpMRI positive and negative patients.** *transperineal or transrectal biopsy approach accepted ^any targeted biopsy approach accepted (fusion/software registration, cognitive, in-bore)	Systematic or template biopsy < 20 cores. Systematic biopsy excludes regions sampled by targeted biopsy. Only mpMRI positive patients underwent biopsy, or only results for mpMRI positive patients reported i.e., no results reported for patients who were mpMRI negative. Radical prostatectomy specimen (restricted to patients with prostate cancer diagnosis).
Outcome	Sensitivity** and specificity^^ for prostate cancer: **ISUP grade ≥ 2 (primary outcome)**, or ISUP grade ≥ 3, or ISUP grade 1 Overall or by age, PSA level or risk subgroups **must report sufficient data to calculate TP and FN for sensitivity ^^must report sufficient data to calculate TN and FP for specificity	PPV, NPV ISUP grade ≥ 2 combined with a subgroup of ISUP grade 1 for example • Maximum CCL ≥5 mm for Gleason score 6 disease Maximum CCL ≥5 mm.
Analyses	Per-patient	Per-lesion
Publication date	From 1st January 1990 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

CCL = cancer core length; DCE = dynamic contrast enhancement; DRE = digital rectal examination; DWI = diffusion weighted imaging; FP = false positive: FN = false negative; ISUP = International Society of Urologic Pathology; MRS = magnetic resonance spectroscopy; PIRADS = Prostate Image-Reporting and Data System; TN = true negative; TP = true positive

1.2 Definitions and terminology

For the purposes of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

False negative refers to individuals with the outcome of interest who were mpMRI negative.

False positive refers to individuals who did not have the outcome of interest who were mpMRI positive.

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).
ISUP grade ≥ 3 prostate cancer is prostate cancer scored as Gleason Score 7(4+3) or higher on histopathological findings (Epstein 2016).
ISUP grade 1 prostate cancer is prostate cancer scored as Gleason Score 6(3+3) on histopathological findings (Epstein 2016).
Multi-parametric MRI (mpMRI) refers to an imaging protocol used to detect and characterise tissue abnormalities to determine the presence and severity of cancer. Prostate mpMRI acquisition includes T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging.
Systematic biopsy includes template and saturation biopsies.
Targeted biopsy refers to a multiparametric MRI-targeted biopsy using cognitive, software registration or in-bore image fusion techniques to identify target/s.

- Cognitive image fusion refers to the operator visually fusing MRI images and real time ultrasound pictures.
- Software registration image fusion refers to using software to fuse uploaded MRI images to real time ultrasound.
- In-bore image fusion refers to fusing prior MRI images and a real time MRI during biopsy.

True negative refers to individuals who did not have the outcome of interest who were mpMRI negative.
True positive refers to individuals with the outcome of interest who were mpMRI positive.

1.3 Guidelines searches

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website

- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, as the evidence for mpMRI triage continues to evolve, be based on literature published up until 2022 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

A search for systematic reviews of prostate mpMRI published from 2010 onwards in Medline, Embase and Cochrane Systematic Review databases (search strategies in Appendix A) yielded 255 records, of which a relevant systematic review by Drost et al (2019) was identified that captured relevant literature published from 1st January 1990 to 31st July 2018. We assessed studies included in the Drost 2019 systematic review for inclusion in our systematic review, and designed searches to identify diagnostic accuracy studies or systematic reviews thereof published from 2018 onwards. Medline (including MEDLINE Epub Ahead of Print,

I-Process & Other Non-Indexed Citations) and Embase databases, and Cochrane Database of Systematic Reviews were searched on 6th December 2023 combining text terms and database-specific subject headings for prostate cancer and multiparametric MRI. Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st September 2024. All searches were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the search is included as Appendix A. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

Two reviewers independently extracted data from the included studies, with independent third-reviewer adjudication if needed. The following study characteristics were extracted: Country and year of publication; participant eligibility and age, PSA level, symptoms, family history of prostate cancer and indication for biopsy; mpMRI details including sequences, magnetic strength, test positivity threshold and scoring system, and radiologist experience; details of biopsies undertaken including number of systematic and targeted cores; prevalence of clinically significant prostate cancer (ISUP grade ≥ 2 cancer); relevant outcomes reported and subgroup data available.

The following data were extracted and used to construct 2x2 tables: total participants with outcome, total without outcome, total index test positive, total index test negative, true positives, false positives, false negatives, and true negatives, for outcomes ISUP grade ≥ 2 prostate cancer, ISUP grade ≥ 3 prostate cancer and ISUP grade 1 prostate cancer, by index test positivity thresholds of PIRADS/Likert ≥ 3 and ≥ 4. The *metadta* command in Stata Version 18.0 (StataCorp 2023) was used to generate study-specific sensitivity and specificity and associated 95% confidence intervals, and summary estimates of sensitivity and specificity, using a fixed model with a 0.5 constant continuity correction for zero counts (Sankey 1996). Forest plots were obtained to present the results graphically. Subgroup analyses were planned for age, PSA level and risk data, if available.

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias of each included study (with independent third-reviewer adjudication as needed) using a modified Quality of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool (Whiting 2011). The overall risk of bias of studies was rated low, moderate, high or unclear based on assessments of the risk of bias associated with the following sources of bias: patient selection, index test, reference standard, and flow and timing.

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for the sensitivity and specificity of multi-parametric MRI to detect the outcomes of interest.
(https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence for each critical outcomes was rated high, moderate, low or very low based on assessment of risk of selection bias, indirectness of the results, imprecision, inconsistency or

heterogeneity of the results and publication bias following GRADE guidance provided by Schunemann 2020a, Schunemann 2020b and Schunemann 2022. Selection bias was considered an important source of bias. Imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. These thresholds were determined by the clinical Working Group and following GRADE guidance provided by Schunemann 2022. Inconsistency was assessed based on the range of point estimates and a consideration of possible sources of heterogeneity. The I^2 statistic was not used to assess heterogeneity as it is designed to assess the heterogeneity of relative proportions not actual proportions and thus could be misleading for sensitivity and specificity estimates. Potential publication bias (or small study effects) was assessed for meta-analyses with 10 or more studies using the nonparametric "trim and fill" method (Duval 2000) implemented using the STATA command "metatrim", following guidance provided by Schunemann 2020b; where there were less than 10 studies, potential conflicts of interest were considered.

As per GRADE guidance, studies started with a high level of certainty in the evidence and were downgraded in a stepwise manner from high to moderate to low to very low if there were serious concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

Definitions of the GRADE ratings of certainty are presented in Appendix B.

2. Results

2.1 Guidelines searches

One potentially relevant guideline was identified which was based on systematic reviews of the literature published up until 2022 or later. It was not considered for adoption as it did not directly consider using mpMRI alone to triage men with elevated PSA levels to biopsy (Appendix C).

2.2 Literature searches

The systematic search for articles published from 2018 onwards identified 4771 unique records to September 1st, 2024 (Figure 1). Of these, 409 potentially relevant full text articles were screened independently by 2 reviewers. 4 additional articles identified from reference lists of included articles, and 16 studies published to 2018 included in the Drost et al (2019) systematic review were screened. Six articles reporting on 5 studies met criteria for inclusion in our systematic review (Hansen 2018, Hogan 2022, Mortezavi 2018, Ahmed 2017, Lovegrove 2020, Bonekamp 2019). There were no studies that included Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.

The retrieved articles that were not included in this update and the reasons for their exclusion are documented in Appendix D. The main reasons for exclusion were no reference standard of interest or no population of interest.

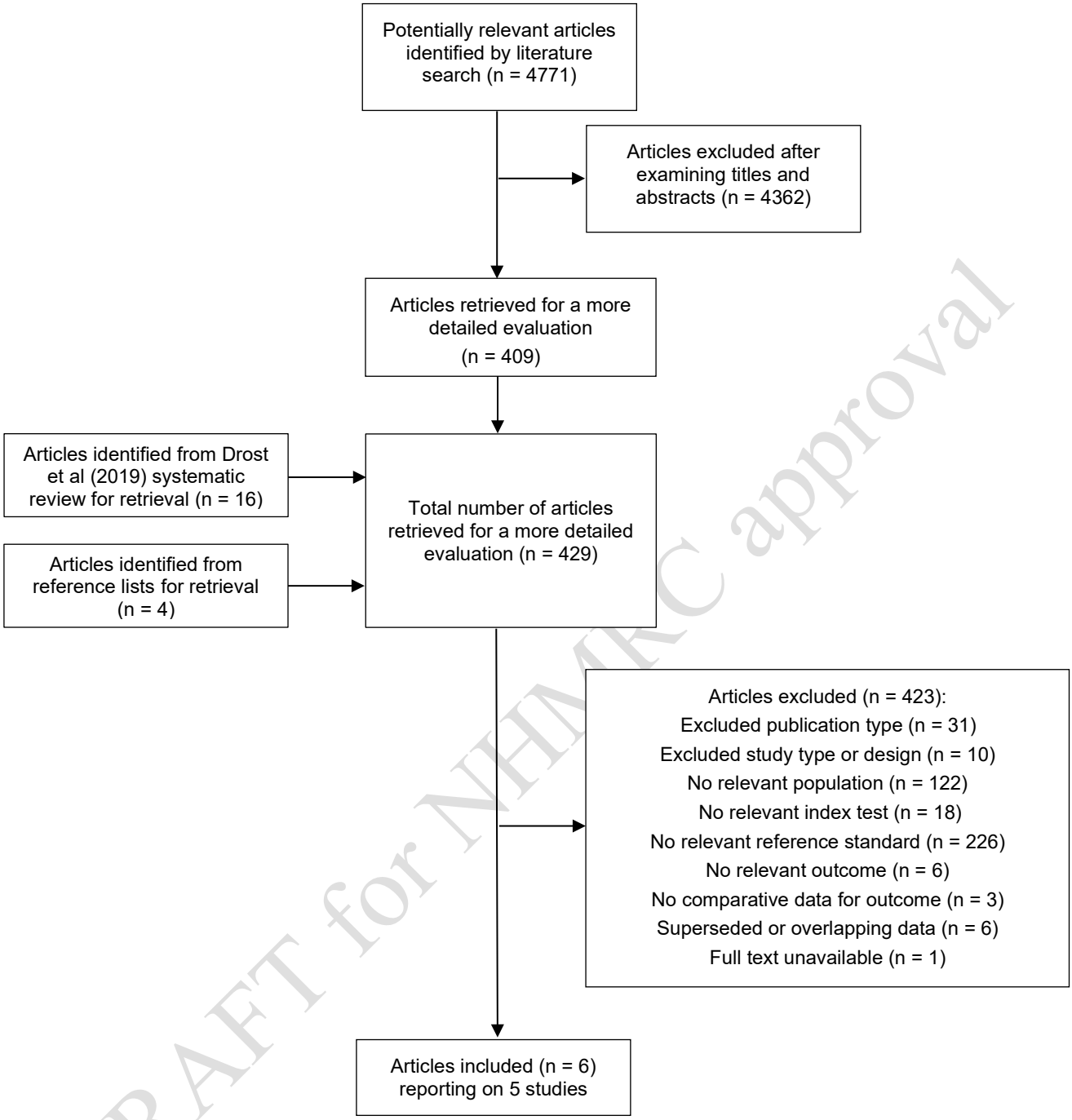

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

2.3 Characteristics of included studies

Table 11. *Study characteristics of included studies of diagnostic accuracy of multiparametric MRI in biopsy naïve men for the detection of clinically significant prostate cancer*

Study	*Participants*	*mpMRI*	*Positive mpMRI*	*Systematic biopsy (SB)*	*Targeted biopsy (TB)*	*Reference standard*	*Prevalence CSPrCa*	*Outcomes of interest*
Hansen 2018 Germany, United Kingdom, Australia Prospective	Men aged <80 years who underwent mpMRI prior to biopsy at multiple tertiary centres in 2012-2016. Indication for biopsy: Elevated PSA (> age-related normal range) 43%, abnormal DRE 6%, elevated PSA and abnormal DRE 43%, other indications including family history 7% **N = 807** Initial biopsy: 100% Age median (IQR): 65 (59-70) years PSA median (IQR): 6.5 (4.9-8.8) ng/ml Symptomatic: NR Family history prostate cancer: NR	T1WI + T2WI + DWI + DCE 1.5 or 3.0T field strength	≥3 on PIRADS v1 (pre-2015) or v2 (2015 onwards) N = 571 (71%) Determined by radiologists with team-based peer-review of images in equivocal cases and ongoing histological feedback on >150 MRI/year.	Transperineal Ginsburg protocol: 3-4 cores per each of 6 prostate sectors using 5mm brachytherapy grid	Transperineal TRUS-**Fusion** TB (2 centres) or **Cognitive** TB (1 centre) Prior to SB ≥2 cores per lesion Median (IQR) **4 (2-5) cores** per patient	**SB+TB** Median (IQR) **26 (24-28) cores** per patient	48.6% (392/807)	**ISUP G ≥ 2** ISUP G ≥ 3 ISUP G = 1 *Reported as Gleason Score* Pathologist blinding NR
Hogan 2022 Australia Retrospective	Men who underwent mpMRI prior to biopsy at a single tertiary centre in 2017-2018. Indication for biopsy: Elevated PSA (threshold and % NR) or abnormal DRE 33% **N = 140** Initial biopsy: 100% Age mean (SD): 61.3 (9.65) years PSA median (IQR): 6 (4.5-8.8) ng/ml Symptomatic: LUTS 45.7% Family history prostate cancer: 14.3%	T1WI + T2WI + DWI + DCE 3.0T field strength with external phased array body coil (>90%)	≥3 on PIRADS v2 N = 97 (69%) Determined by a single radiologist with 7 years' experience reporting on prostate MRIs	Transperineal using 5mm brachytherapy grid Number of cores per patient: NR	Transperineal **Cognitive** TB NR if prior to SB Number of cores per patient: NR 42/97 (43%) mpMRI positive underwent TB. 55/97 had PIRADS 3-5 lesions sampled as part of SB.	**SB+TB** Median (IQR) **26 (22-33) cores** per patient	28.6% (40/140)	**ISUP G ≥ 2** ISUP G ≥ 3 Pathologist blinding NR

Study	*Participants*	*mpMRI*	*Positive mpMRI*	*Systematic biopsy (SB)*	*Targeted biopsy (TB)*	*Reference standard*	*Prevalence CSPrCa*	*Outcomes of interest*
Mortezavi 2018 Switzerland Retrospective	Men who underwent mpMRI prior to biopsy at a single tertiary centre in 2014-2016. Indication for biopsy: NR **N = 163** Initial biopsy: 100% Age median (IQR): 63 (57-68) years PSA median (IQR): 5.8 (4.4-8.9) ng/ml Symptomatic: NR Family history prostate cancer: NR	T2WI + DWI + DCE 3.0T field strength without endorectal coil (84%)	≥3 on 5-point Likert scale N = 114 (70%) Determined by board certified radiologists (number and experience NR)	Transperineal template saturation biopsy according to Barzell zones (20 zones) Median (range) **40 (30-55) cores** per patient	Transperineal TRUS-**Fusion** TB After SB 2-4 cores per lesion Median (IQR) **3 (2-4) cores** per patient	**SB** Median (range) **40 (30-55) cores** per patient	47% (77/163)	**ISUP G ≥ 2** ISUP G ≥ 3 ISUP G = 1 *Reported as Gleason Score* Pathologist blinding NR
Ahmed 2017 and **Lovegrove 2020** **PROMIS** (Prostate MR Imaging Study) United Kingdom Prospective	Men aged >18 years who underwent mpMRI prior to biopsy at multiple (11) centres in 2012-2015. Excluded men with prostate volume >100ml. Indication for biopsy: Elevated PSA (≤15 ng/ml), abnormal DRE, suspected organ confined stage ≤ T2 on rectal examination, or family history (% NR) **N = 576** Initial biopsy: 100% Age mean (± SD): 63.4 (± 7.6) years PSA mean (± SD): 7.1 (± 2.9) ng/ml Symptomatic: NR? Family history prostate cancer: 22% (127/569 data available)	T1WI + T2WI + DWI + DCE 1.5T field strength with pelvic phased array coil	≥3 on 5-point Likert scale N = 418 (73%) Determined by experienced urologic-radiologists who underwent study-specific centralised training of reporting prostate MRIs	Transperineal template mapping biopsy sampling every 5mm Estimated >40 cores per patient (Drost 2019) *Patients then underwent 10-12 core TRUS biopsy – results not relevant to this systematic review*	TB not performed	**SB** Estimated **>40 cores** (median NR) per patient (Drost 2019)	53% (308/576)	**ISUP G ≥ 2** ISUP G ≥ 3 ISUP G = 1 *Reported as Gleason Score* Pathologist **blinded** to all test results
Bonekamp 2019 Germany Retrospective	Men who underwent mpMRI prior to biopsy at a single centre in 2015-2016. Indication for biopsy: Elevated PSA or clinical examination (% NR) **N = 173** Initial biopsy: 100% Age median (IQR): NR [64 (58-71) years for overall study cohort] PSA median (IQR): NR Symptomatic: NR Family history prostate cancer: NR	T2WI + DWI + DCE 3T field strength with body coil and spine phased array coil	≥3 on PIRADS v2 N = 149 (86%) Determined by radiologists (number and experience NR)	Transperineal saturation biopsy (Ginsburg protocol) Median (range) **23 (20-26) cores** per patient	Transperineal TRUS-**Fusion** TB Prior to SB Median (range) **4 (3-5) cores** per *lesion*	**SB+TB** Median (range) **29 (24-33) cores** per patient	46% (80/173)	**ISUP G ≥ 2** ISUP G ≥ 3 *Reported as Gleason Score* Pathologist blinding NR

3T = 3 tesla; CSPrCa = clinically significant prostate cancer; DCE = dynamic contrast enhancement; DRE = digital rectal examination; DWI = diffusion weighted imaging; IQR = interquartile range ISUP G = International Society of Urological Pathology grade; LUTS = lower urinary tract symptoms; NR = not reported; PIRADS = Prostate Image-Reporting and Data System; SB = systematic biopsy; SD = standard deviation; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging; TB = MRI-targeted biopsy; TRUS = transrectal ultrasound

2.4 Results by outcomes of interest

Results for diagnostic performance (sensitivity and specificity) related to the detection of

ISUP grade ≥ 2 prostate cancer – Table 4, Figures 2 & 3

ISUP grade ≥ 3 prostate cancer – Table 5, Figures 4 & 5

ISUP grade 1 prostate cancer – Table 6, Figures 6 & 7

1. *Results for the detection of* ***clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer)***

Table 12. *Sensitivity and specificity of mpMRI in biopsy naïve individuals for the detection of* ***clinically significant prostate cancer*** *(ISUP grade ≥ 2 prostate cancer)*

Analysis	***Figure***	***Studies (N)***	***Participants (N)***	***ISUP grade ≥ 2 prostate cancer*** *per 1000 individuals*	***Triage scenario: mpMRI-positivity threshold for biopsy***	***Sensitivity*** *(95%CI)*	***Specificity*** *(95% CI)*
Meta-analysis	2	5 (6 articles)	1859	483	PIRADS/Likert ≥3	0.89 (0.86, 0.91)	0.42 (0.39, 0.46)
Meta-analysis	3	5 (6 articles)	1859	483	PIRADS/Likert ≥4	0.74 (0.71, 0.77)	0.73 (0.70, 0.76)

CI = confidence interval; ISUP = International Society of Urological Pathology; mpMRI = multi-parametric magnetic resonance imaging; N = number; PIRADS = Prostate Image-Reporting and Data System

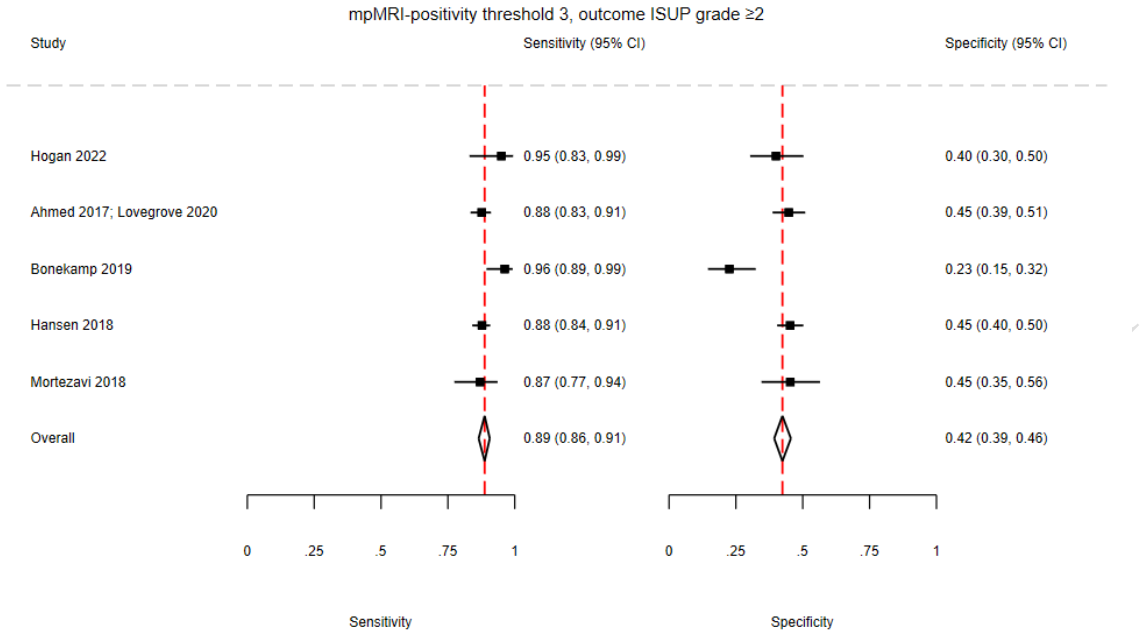

Figure 2. *mpMRI-positivity threshold 3, outcome ISUP grade ≥2*
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

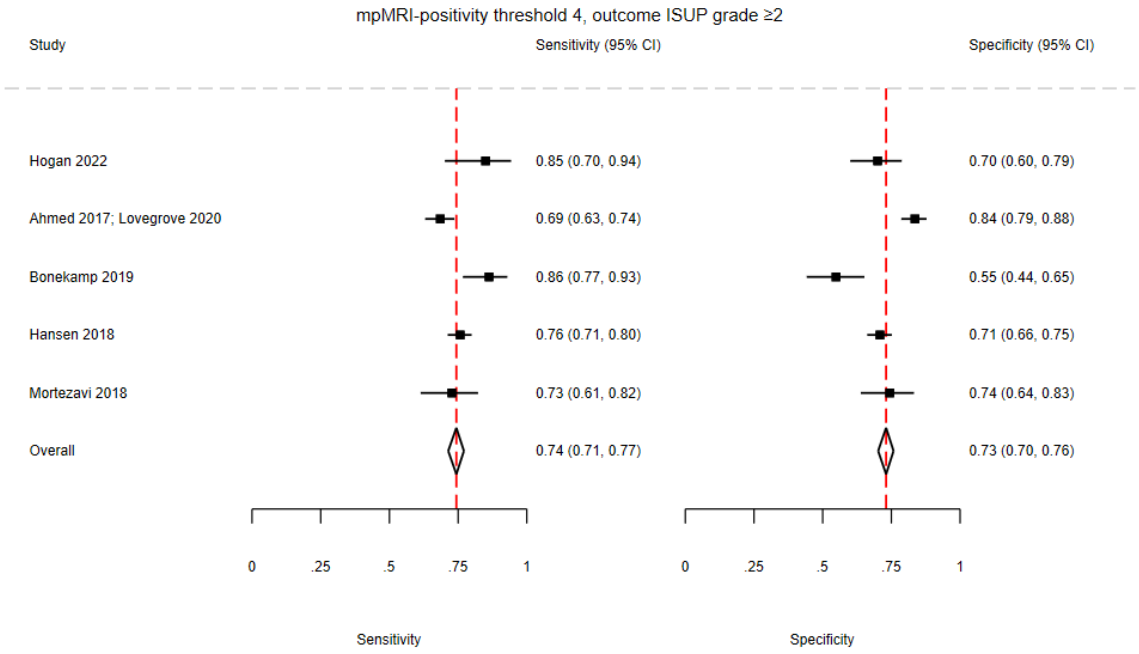

Figure 3. *mpMRI-positivity threshold 4, outcome ISUP grade ≥2*
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

*2. Results for the detection of **ISUP grade ≥ 3 prostate cancer***

Table 13. *Sensitivity and specificity of mpMRI in biopsy naïve men for the detection of ISUP grade ≥ 3 prostate cancer*

Analysis	***Figure***	***Studies (N)***	***Participants (N)***	***ISUP grade ≥ 3 prostate cancer*** *per 1000 individuals*	***Triage scenario: mpMRI-positivity threshold for biopsy***	***Sensitivity*** *(95%CI)*	***Specificity*** *(95% CI)*
Meta-analysis	4	5 (6 articles)	1859	169	PIRADS/Likert ≥3	0.95 (0.92, 0.97)	0.32 (0.30, 0.34)
Meta-analysis	5	4 (5 articles)	1696	160	PIRADS/Likert ≥4	0.90 (0.85, 0.93)	0.58 (0.55, 0.60)

CI = confidence interval; ISUP = International Society of Urological Pathology; mpMRI = multi-parametric magnetic resonance imaging; N = number; PIRADS = Prostate Image-Reporting and Data System

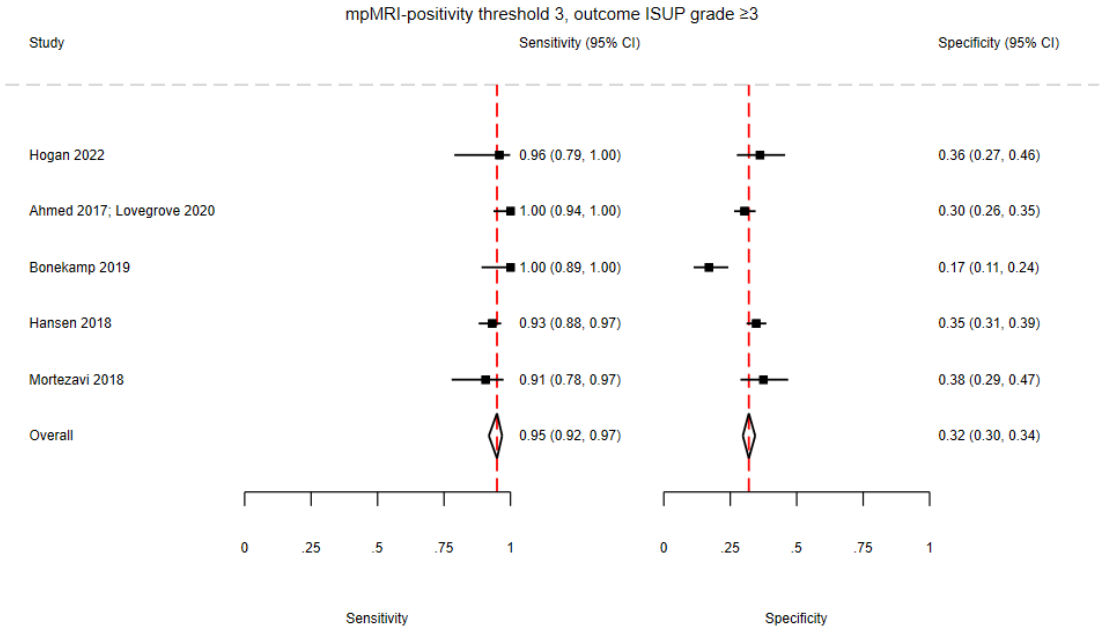

Figure 4. *mpMRI-positivity threshold 3, outcome ISUP grade ≥3*
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

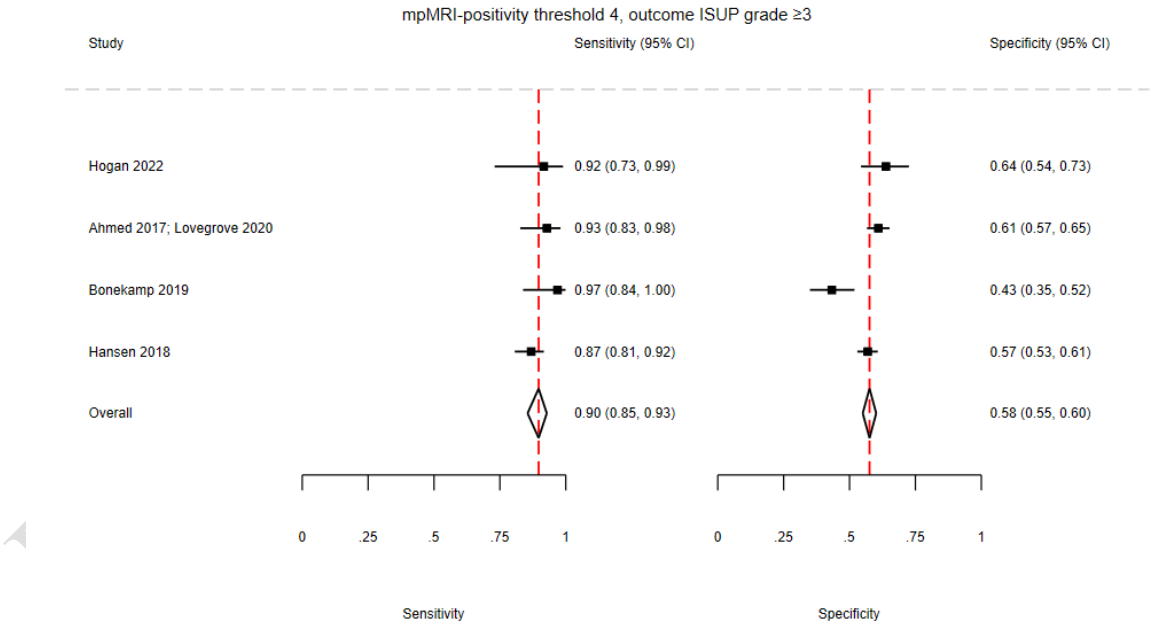

Figure 5. *mpMRI-positivity threshold 4, outcome ISUP grade ≥3*
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

*3. Results for the detection of **ISUP grade 1 prostate cancer***

Table 14. *Sensitivity of mpMRI in biopsy naïve men for the detection of ISUP grade 1 prostate cancer*

Analysis	***Figure***	***Studies (N)***	***Participants (N)***	***ISUP grade 1 prostate cancer*** *per 1000 individuals*	***Triage scenario: mpMRI-positivity threshold for biopsy***	***Sensitivity*** *(95% CI)***
Meta-analysis	6	3 (4 articles)	1546	179	PIRADS/Likert ≥3	0.68 (0.62, 0.73)
Meta-analysis	7	2 (3 articles)	1383	184	PIRADS/Likert ≥4	0.37 (0.31, 0.43)

CI = confidence interval; *ISUP = International Society of Urological Pathology;* mpMRI = multi-parametric magnetic resonance imaging; N = number; *PIRADS = Prostate Image-Reporting and Data System*

***Specificity not calculated as false positives and true negatives include count of 'no cancer' and ISUP grade ≥2 prostate cancers*

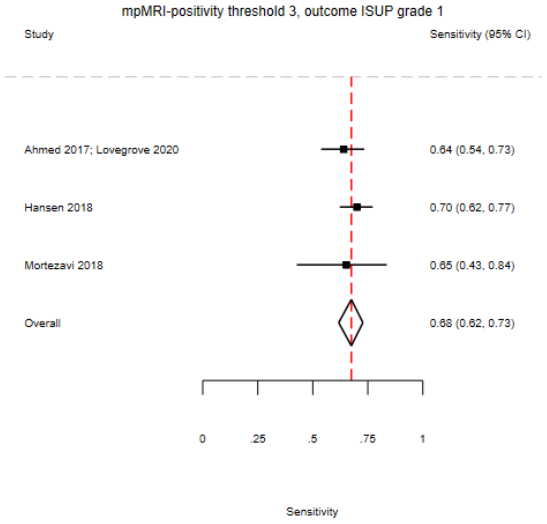

Figure 6. *mpMRI-positivity threshold 3, outcome ISUP grade 1*
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

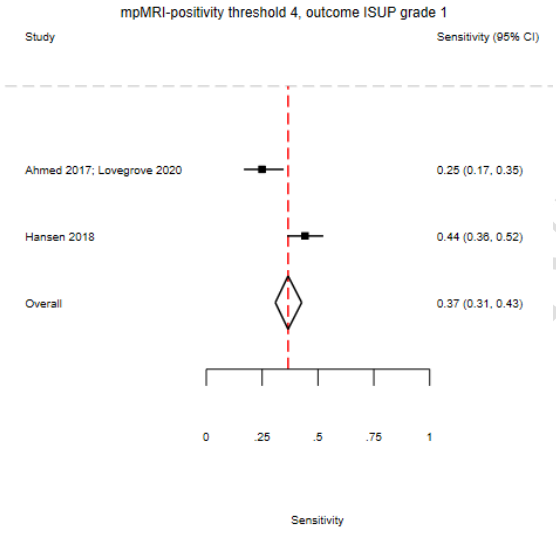

Figure 7. *mpMRI-positivity threshold 4, outcome ISUP grade 1*
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

2.5 Risk of bias

The results of the risk of bias assessments for the included studies are shown in Table 7.

Table 15. *Risk of bias assessments for included diagnostic accuracy studies using the Quality of Diagnostic Accuracy Studies-2 (QUADAS-2) risk of bias assessment tool (Whiting 2011).*

Study	Risk of bias (QUADAS-2)				
	Patient selection	Index test	Reference standard	Flow and Timing	Overall
Hansen 2018	High	Low	Moderate	High	High
Hogan 2022	High	Low	Moderate	High	High
Mortezavi 2018	High	Low	Unclear	Low	High
Bonekamp 2019	High	Low	Moderate	High	High
Ahmed 2017; Lovegrove 2020	High	Low	Low	Low	High

3. GRADE assessment of the certainty of the evidence

ISUP grade ≥ 2 prostate cancer – assessments are shown in Table 8

ISUP grade ≥ 3 prostate cancer – assessments are shown in Table 9

ISUP grade 1 prostate cancer – assessments are shown in Table 10

Table 16. *GRADE assessment of the certainty of the evidence for the sensitivity and specificity of multiparametric MRI to detect ISUP Grade ≥ 2 prostate cancer*

	Rating	***Reason for downgrading***	***Certainty of evidence***
mpMRI-positivity threshold of 3 (Figure 2)			
Risk of bias	Serious concerns (-1)	All 5 studies at high risk of selection bias.	
Indirectness	No serious concerns	One of five studies reported > 40% of population symptomatic. The remaining 4 studies did not report whether patients asymptomatic or symptomatic. The prevalence of clinically significant disease in these studies was almost double that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of MRI	
Imprecision	*Sensitivity* No serious concerns *Specificity* No serious concerns	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals, undergoing triage using a mpMRI-positivity threshold of 3, 23 (18-28) ISUP Grade ≥ 2 prostate cancers not detected and 339 (312-368) unnecessary biopsies avoided. For ISUP Grade ≥ 2 prostate cancer not detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI did not cross any thresholds. For unnecessary biopsies avoided using a MCID of 100/1000 and thresholds for moderate and large effects of 200/1000 and 400/1000, the 95%CI did not cross any thresholds.	***Sensitivity*** **Moderate** ***Specificity*** **Moderate**
Inconsistency	No serious concerns	Range of point estimates ≤ 10 percentage points for sensitivity > 10 percentage points between highest and lowest point estimates for specificity. Bonekamp 2019 reported much lower specificity but higher sensitivity suggesting a more risk averse approach to MRI interpretation than in the other studies.	
Publication bias	Not detected	All 5 studies either reported no direct funding by industry and/or declared no conflicts of interest.	
mpMRI-positivity threshold of 4 (Figure 3)			
Risk of bias	Serious concerns (-1)	All 5 studies at high risk of selection bias.	
Indirectness	No serious concerns	One of five studies reported > 40% of population symptomatic. The remaining 4 studies did not report whether patients asymptomatic or symptomatic. The prevalence of clinically significant disease in these studies was almost double that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of MRI	***Sensitivity*** **Low** ***Specificity*** **Moderate**
Imprecision	*Sensitivity* Serious concerns (-1) *Specificity* No serious concerns	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals, undergoing triage using a mpMRI-positivity threshold of 4, 51 (46-58) ISUP Grade ≥ 2 prostate cancers not detected and 585 (560-608) unnecessary biopsies avoided. For ISUP Grade ≥ 2 prostate cancer not detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000, the 95%CI crossed one threshold. For unnecessary biopsies avoided using a MCID of 100/1000 and thresholds for moderate and large effects of 200/1000 and 400/1000, the 95%CI did not cross any thresholds.	
Inconsistency	No serious concerns	Range of point estimates > 10 percentage points for sensitivity. Higher sensitivities were reported by the two studies, Bonekamp 2019 and Hogan 2022, that used PIRADS version 2 exclusively.	

		Greater than 10 percentage points between highest and lowest point estimates for specificity. Bonekamp 2019 reported much lower specificity but higher sensitivity suggesting a more risk averse approach to MRI interpretation than in the other studies.	
Publication bias	Not detected	All 5 studies either reported no direct funding by industry and/or declared no conflicts of interest.	

CI = confidence interval; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; mpMRI = multiparametric MRI

Table 17. *GRADE assessment of the certainty of the evidence for the sensitivity of multiparametric MRI to detect ISUP Grade ≥ 3 prostate cancer*

	Rating	***Reason for downgrading***	***Certainty of evidence***
mpMRI-positivity threshold of 3 (Figure 4)			
Risk of bias	Serious concerns (-1)	All 5 studies at high risk of selection bias.	***Sensitivity*** **Moderate**
Indirectness	No serious concerns	One of five studies reported > 40% of population symptomatic. The remaining 4 studies did not report whether patients asymptomatic or symptomatic. The prevalence of clinically significant disease in these studies was almost double that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of MRI	
Imprecision	No Serious concerns	If prevalence of ISUP Grade ≥ 3 prostate cancer is 10%, in a population of 1000 individuals, undergoing triage using a mpMRI-positivity threshold of 3, 5 (3-8) ISUP Grade ≥ 3 prostate cancers not detected. For ISUP Grade ≥ 3 prostate cancer not detected, using a MCID of 35/1000 and thresholds for moderate and large effects of 70/1000 and 140/1000 the 95%CI did not cross any thresholds. If prevalence of ISUP Grade ≥ 3 prostate cancer is 20%, in a population of 1000 individuals, undergoing triage using a mpMRI-positivity threshold of 3, 10 (6-18) ISUP Grade ≥ 3 prostate cancers not detected. For ISUP Grade ≥ 3 prostate cancer not detected, using a MCID of 35/1000 and thresholds for moderate and large effects of 70/1000 and 140/1000, the 95%CI did not cross any thresholds.	
Inconsistency	No serious concerns	Range of point estimates <10 percentage points for sensitivity.	
Publication bias	Not detected	All 5 studies either reported no direct funding by industry and/or declared no conflicts of interest.	
mpMRI-positivity threshold of 4 (Figure 5)			
Risk of bias	Serious concerns (-1)	All 4 studies at high risk of selection bias.	***Sensitivity*** **Moderate**
Indirectness	No serious concerns	One of four studies reported > 40% of population symptomatic. The remaining 4 studies did not report whether patients asymptomatic or symptomatic. The prevalence of clinically significant disease in these studies was almost double that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of MRI	
Imprecision	No serious concerns	If prevalence of ISUP Grade ≥ 3 prostate cancer is 10%, in a population of 1000 individuals, undergoing triage using a mpMRI-positivity threshold of 4, 10 (7-15) ISUP Grade ≥ 3 prostate cancers not detected. For ISUP Grade ≥ 3 prostate cancer not detected using a MCID of 35/1000 and thresholds for moderate and large effects of 70/1000 and 140/1000, the 95%CI did not cross any thresholds. If prevalence of ISUP Grade ≥ 3 prostate cancer is 20%, in a population of 1000 individuals, undergoing triage using a mpMRI-positivity threshold of 4, 21 (14-30) ISUP Grade ≥ 3 prostate cancers not detected. For ISUP Grade ≥ 3 prostate cancer not detected, using a MCID of 35/1000 and thresholds for moderate and large effects of 70/1000 and 140/1000, the 95%CIs did not cross any thresholds.	
Inconsistency	No serious concerns	Range of point estimates ≤10 percentage points for sensitivity.	
Publication bias	Not detected	All 4 studies either reported no direct funding by industry and/or declared no conflicts of interest.	

CI = confidence interval; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; mpMRI = multiparametric MRI

Table 18. *GRADE assessment of the certainty of the evidence for the sensitivity of multiparametric MRI to detect ISUP Grade 1 prostate cancer*

	Rating	***Reason for downgrading***	***Certainty of evidence***
mpMRI-positivity threshold of 3 (Figure 6)			
Risk of bias	Serious concerns (-1)	All 3 studies at high risk of selection bias.	***Sensitivity*** **Moderate**
Indirectness	No serious concerns	None of the 3 studies reported whether patients asymptomatic or symptomatic. The prevalence of clinically significant disease in these studies was almost double that in a study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of MRI.	
Imprecision	No serious concerns	If prevalence of ISUP Grade 1 prostate cancer is 20%, in a population of 1000 individuals, undergoing triage using a mpMRI-positivity threshold of 3, 64 (54-76) ISUP Grade 1 prostate cancers not detected. For ISUP Grade 1 prostate cancer not detected, using a MCID of 100/1000 and thresholds for moderate and large effects of 200/1000 and 400/1000, the 95%CI did not cross any thresholds.	
Inconsistency	No serious concerns	Range of point estimates <10 percentage points for sensitivity	
Publication bias	Not detected	All 3 studies either reported no direct funding by industry and/or declared no conflicts of interest	
mpMRI-positivity threshold of 4 (Figure 7)			
Risk of bias	Serious concerns (-1)	Both studies at high risk of selection bias.	***Sensitivity*** **Moderate**
Indirectness	No serious concerns	Neither study reported whether patients asymptomatic or symptomatic. The prevalence of clinically significant disease in both studies was almost double that in a study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of MRI.	
Imprecision	No serious concerns	If prevalence of ISUP Grade 1 prostate cancer is 20%, in a population of 1000 individuals, undergoing triage using a mpMRI-positivity threshold of 4, 127 (114-138) ISUP Grade 1 prostate cancers not detected. For ISUP Grade 1 prostate cancer not detected, using a MCID of 100/1000 and thresholds for moderate and large effects of 200/1000 and 400/1000, the 95%CI did not cross any thresholds.	
Inconsistency	No serious concerns	Range of point estimates >10 percentage points for sensitivity. Differences in sensitivity could be explained by the use of MRI-targeted biopsies; the study reporting higher sensitivity (Hansen 2018) undertook MRI-targeted biopsies whereas the study reporting lower sensitivity (Ahmed 2017 & Lovegrove 2020) did not.	
Publication bias	Not detected	Both studies either reported no direct funding by industry and/or declared no conflicts of interest.	

CI = confidence interval; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; mpMRI = multiparametric MRI

4. Summary of findings

Table 19. *Summary of findings for different protocols for triaging men to biopsy using mpMRI when compared to no triage to biopsy (i.e. all men undergo biopsy regardless of MRI result), if the prevalence amongst men with elevated PSA levels of ISUP Grade ≥ 2 and ISUP Grade 1 is 10%, 20% or 30%, and of ISUP Grade ≥ 3 is 10% or 20%.*

Outcome	***Studies (Participants)***	***Certainty of the evidence (GRADE)***	***Triage protocol:*** *mpMRI positive threshold for biopsy*	***Summary sensitivity*** *(95% CI)*	***Summary specificity*** *(95% CI)*	***Implications in a population of 1000 individuals with elevated PSA levels with disease prevalence^ of:***									***Plain text summary##***
						10%			***20%***			***30%***			
						csPrCas undetected (95% CI)	*Unnecessary biopsies avoided (95% CI)*	*NPV*	*csPrCas undetected (95% CI)*	*Unnecessary biopsies avoided (95% CI)*	*NPV*	*csPrCas undetected (95% CI)*	*Unnecessary biopsies avoided (95% CI)*	*NPV*	Using mpMRI to triage men to biopsy increases the number of clinically significant cancers undetected and the number of unnecessary biopsies avoided when compared to no triage
ISUP Grade ≥ 2	5 (1859)	Moderate [a]	PIRADS/ Likert ≥3	0.887 (0.86, 0.91)	0.424 (0.39, 0.46)	11 (9, 14)	382 (351, 414)	0.971	23 (18, 28)	339 (312, 368)	0.936	34 (27, 42)	297 (273, 322)	0.897	If do not biopsy men with a PIRADS of 1-2 the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant** and the number of unnecessary biopsies avoided is likely moderate#
	5 (1859)	*Sensitivity* Low [b] *Specificity* Moderate [a]	PIRADS/ Likert ≥4	0.744 (0.71, 0.77)	0.731 (0.70, 0.76)	26 (23, 29)	658 (630, 684)	0.962	51 (46, 58)	585 (560, 608)	0.920	77 (69, 87)	512 (490, 532)	0.869	If do not biopsy men with a PIRADS of 1-3 the number of undetected ISUP Grade ≥ 2 prostate cancers may be small but clinically important** and the number of unnecessary biopsies avoided is likely large#
ISUP Grade ≥ 3	5 (1859)	Moderate [a]	PIRADS/ Likert ≥3	0.949 (0.92, 0.97)	0.320 (0.30, 0.34)	5 (3, 8)		0.983	10 (6, 16)		0.962				If do not biopsy men with a PIRADS of 1-2 the number of undetected ISUP Grade ≥ 3 prostate cancers is likely clinically unimportant *^
	4 (1696)	Moderate [a]	PIRADS/ Likert ≥4	0.897 (0.85, 0.93)	0.576 (0.55, 0.60)	10 (7, 15)		0.981	21 (14, 30)		0.956				If do not biopsy men with a PIRADS of 1-3 the number of undetected ISUP Grade ≥ 3 prostate cancers is likely clinically unimportant*^
						ISUP Grade 1 undetected (95% CI)	NA*	NA*	*ISUP Grade 1 undetected (95% CI)*	NA*	NA*	*ISUP Grade 1 undetected (95% CI)*	NA*	NA*	
ISUP Grade 1	3 (1546)	Moderate [a]	PIRADS/ Likert ≥3	0.675 (0.62, 0.73)	NA*	32 (27, 38)			64 (54, 76)			97 (81, 114)			If do not biopsy men with a PIRADS of 1-2 the number of undetected ISUP Grade 1 prostate cancers is likely clinically unimportant^^
	2 (1383)	Moderate [a]	PIRADS/ Likert ≥4	0.366 (0.31, 0.43)	NA*	63 (57, 69)			127 (114, 138)			190 (171, 207)			If do not biopsy men with a PIRADS of 1-3 the number of undetected ISUP Grade 1 prostate cancers is likely small but clinically important ^^

CI = confidence interval; csPrCa = clinically significant prostate cancer; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; NA = not available; NPV = negative predictive value; PIRADS = Prostate Image-Reporting and Data System

Clinically significant cancers undetected are the number ISUP grade ≥ 2 or ≥ 3 prostate cancers not detected by the index test (false negatives); this is a non-desirable outcome of mpMRI triage.
The number of ISUP grade 1 prostate cancers not detected on mpMRI is considered a desirable outcome of mpMRI triage.
Unnecessary biopsies avoided are the number of mpMRI negative (mpMRI results below the specified threshold for biopsy) individuals without ISUP grade ≥ 2 prostate cancers detected (true negatives) for whom it would be acceptable to avoid biopsy; this is a desirable outcome of mpMRI triage.
NPV is the proportion of individuals for whom the outcome of interest was not detected (true negatives) among the total number of mpMRI negative individuals. Note this metric is dependent on the underlying prevalence of the outcome.
**Specificity not calculated for ISUP grade 1 prostate cancer as false positives and true negatives count 'no cancer' and ISUP grade ≥2 prostate cancers. Unnecessary biopsies avoided and NPV therefore not calculated for this outcome.*
^ Implications are calculated for a range of prevalences as there are no data on the prevalence of any of these outcomes in populations of individuals with elevated PSA levels in Australia
Based on an outcome prevalence of 20%
*** Using thresholds of 50, 100 and 200 undetected ISUP Grade ≥ 2 prostate cancer/1000 for small (MCID), moderate and large effects*
**^ Using thresholds of 35, 70 and 140 undetected ISUP Grade ≥ 3 prostate cancer/1000 for small (MCID), moderate and large effects*
^^ Using thresholds of 100, 200 and 400 undetected ISUP Grade 1 prostate cancer/1000 for small (MCID), moderate and large effects
 # Using thresholds of 100, 200 and 400 unnecessary biopsies avoided /1000 for small (MCID), moderate and large effects
[a] Serious concerns re potential selection bias
[b] Serious concerns re potential selection bias and imprecision

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APPENDICES

Appendix A: Literature search strategies

A.1 Search strategies for systematic reviews published 2010 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2010 -Current"
20	(Systematic* adj3 review*).tw.
21	(meta-analys* or meta analys*).tw.
22	20 or 21
23	19 and 22
24	remove duplicates from 23

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2010 and Jan 2024, in Cochrane Reviews (Word variations have been searched)

A.2 Search strategies for primary studies published 2018 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	from 19 keep 1-6000
21	remove duplicates from 20
22	from 19 keep 6001-7458
23	remove duplicates from 22
24	21 or 23
25	remove duplicates from 24

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2018 and Jan 2025, in Cochrane Reviews (Word variations have been searched)

Appendix B: GRADE assessment of the certainty of the evidence

Ratings	*Definitions*
⨁⨁⨁⨁ High certainty	The panel is very confident that the true effect lies close to that of the estimate of the effect
⨁⨁⨁◯ Moderate certainty	The panel is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁◯◯ Low certainty	The panel's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁◯◯◯ Very low certainty	The panel has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reportedly based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Did not directly consider using mpMRI alone to triage men to biopsy

Appendix D: Excluded Studies

Article	*DOI/Link*	*Reason for exclusion*
Articles from primary studies search and citation searching		
Abe 2023	https://dx.doi.org/10.1016/j.prnil.2023.08.002	No relevant population
Ahdoot 2022	https://dx.doi.org/10.1016/j.euo.2021.03.004	No relevant population
Akpinar 2024	https://dx.doi.org/10.1016/j.clgc.2024.102071	No relevant reference standard
Al Hussein Al Awamlh 2021	https://dx.doi.org/10.1056/NEJMc2115775	Excluded publication type
Alkema 2022	https://dx.doi.org/10.1016/j.euros.2022.08.005	No relevant reference standard
Altay 2022	https://dx.doi.org/10.5152/eurasianjmed.2022.20349	No relevant reference standard
Amini 2024	https://dx.doi.org/10.1016/j.euo.2024.01.015	No relevant reference standard
Arafa 2021	https://dx.doi.org/10.1016/j.prnil.2021.01.001	No relevant population
Arik 2022	https://dx.doi.org/10.56434/j.arch.esp.urol.20227505.60	No relevant reference standard
Arulraj 2024	https://dx.doi.org/10.1016/j.prnil.2024.03.005	No relevant reference standard
Aslanoglu 2024	https://dx.doi.org/10.4274/uob.galenos.2023.2023.6.2	No relevant population
Avolio 2024	https://dx.doi.org/10.5489/cuaj.8675	No relevant reference standard
Baba 2021	https://dx.doi.org/10.4274/uob.galenos.2021.2021.4.4	No relevant reference standard
Baboudjian 2020	https://dx.doi.org/10.1007/s11255-019-02353-5	No relevant reference standard
Baghdanian 2019	https://dx.doi.org/10.1590/0100-3984.2018.0126	No relevant population
Bahlburg 2023	https://dx.doi.org/10.1159/000529946	No relevant reference standard
Bai 2020	https://dx.doi.org/10.2147/CMAR.S257769	No relevant population
Bajeot 2022	https://dx.doi.org/10.1016/j.euo.2021.06.001	No relevant population
Ballon 2020	https://dx.doi.org/10.1097/UPJ.0000000000000124	No relevant population
Bang 2021	https://dx.doi.org/10.1038/s41598-021-00548-4	No relevant population
Bangash 2021	https://dx.doi.org/10.53350/pjmhs2115102625	No relevant reference standard
Bao 2021	https://dx.doi.org/10.1002/jmri.27394	No relevant reference standard
Barnett 2018	https://dx.doi.org/10.1111/bju.14151	Excluded study design
Barone 2023	https://dx.doi.org/10.3390/diagnostics13111939	No relevant reference standard
Baroni 2019	https://dx.doi.org/10.1590/0100-3984.2019.52.5e1	Excluded publication type
Barrett 2019	https://dx.doi.org/10.1016/j.crad.2019.06.004	No relevant reference standard
Barry 2018	https://dx.doi.org/10.1056/NEJMe1804231	Excluded publication type
Barth 2021	https://dx.doi.org/10.1016/j.ejro.2021.100332	No relevant population
Baruah 2019	https://dx.doi.org/10.14740/wjon1230	No relevant reference standard
Bass 2018	https://dx.doi.org/10.1136/bmjopen-2018-024941	No relevant reference standard
Bastian-Jordan 2018	https://dx.doi.org/10.1111/1754-9485.12678	No relevant population
Baudewyns 2024	https://dx.doi.org/10.1007/s00345-024-04962-x	No relevant population
Baumgartner 2019	https://dx.doi.org/10.1016/j.humpath.2019.04.016	No relevant population
Benelli 2020	https://dx.doi.org/10.1177/1756287220916613	No relevant population
Benidir 2023	https://dx.doi.org/10.1016/j.urology.2023.03.014	No relevant reference standard
Berg 2022	https://dx.doi.org/10.1159/000520598	No relevant reference standard
Berkenwald 2021	https://pubmed.ncbi.nlm.nih.gov/34129464/	No relevant reference standard
Bertolo 2021	https://dx.doi.org/10.1016/j.purol.2020.12.008	No relevant reference standard
Bevill 2022	https://dx.doi.org/10.1016/j.urolonc.2021.05.029	No relevant reference standard
Bey 2018	https://dx.doi.org/10.5489/cuaj.4571	No relevant reference standard
Bhambri 2020	https://dx.doi.org/10.7860/JCDR/2020/45298.31898	No relevant reference standard
Bhat 2019	https://dx.doi.org/10.1016/j.urology.2018.12.010	No relevant reference standard

Bhat 2020	https://dx.doi.org/10.1080/13685538.2019.1641796	No comparative data for outcome
Bittencourt 2022	https://dx.doi.org/10.1007/s00330-021-08407-6	No relevant reference standard
Boesen 2019	https://dx.doi.org/10.1016/j.euo.2018.09.001	No relevant index test
Boeve 2023	https://dx.doi.org/10.1111/bju.16041	No relevant population
Bogner 2022	https://dx.doi.org/10.1007/s00261-022-03444-1	No relevant population
Borkowetz 2018	https://dx.doi.org/10.1111/bju.14017	No relevant reference standard
Bosaily 2020	https://dx.doi.org/10.1016/j.eururo.2020.03.002	Overlapping data
Boschheidgen 2024	https://dx.doi.org/10.1016/j.eururo.2023.09.027	No relevant reference standard
Brembilla 2023	https://dx.doi.org/10.1016/j.ejrad.2023.110849	No relevant reference standard
Briggs 2021	https://dx.doi.org/10.1016/j.urology.2021.04.040	No relevant population
Brown 2018	https://dx.doi.org/10.3310/hta22390	Excluded publication type
Bryant 2019	https://dx.doi.org/10.1016/j.juro.2018.09.049	No relevant reference standard
Burk 2023	https://dx.doi.org/10.1016/j.jacr.2023.02.034	No relevant population
Busetto 2021	https://dx.doi.org/10.1007/s00345-020-03359-w	No relevant reference standard
Buteau 2024	https://doi.org/10.1016/j.euo.2023.11.008	Excluded publication type
Byun 2022	https://dx.doi.org/10.1016/j.prnil.2021.10.002	No relevant index test
Cai 2021	https://dx.doi.org/10.3390/curroncol28030169	No relevant reference standard
Campistol 2022	https://dx.doi.org/10.3390/cancers14112702	No relevant reference standard
Carbunaru 2021	https://dx.doi.org/10.1002/bco2.91	No relevant reference standard
Chaloupka 2020	https://dx.doi.org/10.1007/s00117-020-00716-z	Excluded publication type
Chaloupka 2023	https://dx.doi.org/10.3233/CH-238101	No relevant population
Chang 2024	https://dx.doi.org/10.1097/JCMA.0000000000001117	No relevant population
Charalampos 2020	https://dx.doi.org/10.4103/iju.IJU_182_20	Excluded publication type
Chau 2018	https://dx.doi.org/10.1016/j.ijso.2018.01.002	No relevant population
Chau 2023	https://dx.doi.org/10.1177/20514158211065949	No relevant reference standard
Checcucci 2020	https://dx.doi.org/10.23736/S0393-2249.20.03958-2	No relevant population
Chen 2021	https://dx.doi.org/10.1016/j.clgc.2020.12.007	No relevant reference standard
Chen 2021	https://dx.doi.org/10.3389/fonc.2021.792456	No relevant reference standard
Chen 2022	https://dx.doi.org/10.3389/fonc.2022.994296	No relevant reference standard
Cheng 2023	https://dx.doi.org/10.21037/tau-22-832	No relevant reference standard
Cheng 2024	https://dx.doi.org/10.1186/s13244-023-01544-0	No relevant population
Chiu 2023	https://dx.doi.org/10.4103/UROS.UROS_33_22	No relevant reference standard
Chiu 2023	https://dx.doi.org/10.1097/JU.0000000000003450	No relevant reference standard
Chiu 2023	https://dx.doi.org/10.4103/aja20239	No relevant reference standard
Choe 2023	https://dx.doi.org/10.1016/j.urology.2022.09.007	No relevant population
Choi 2019	https://dx.doi.org/10.1016/j.crad.2019.02.002	No relevant population
Choi 2023	https://dx.doi.org/10.1016/j.acra.2022.07.020	No relevant reference standard
Colvin 2021	https://dx.doi.org/10.1016/j.clinimag.2021.09.003	No relevant reference standard
Cussenot 2023	https://dx.doi.org/10.1111/bju.15968	No relevant reference standard
Dagnino 2024	https://dx.doi.org/10.1016/j.urolonc.2024.06.021	No relevant reference standard
Dahl 2024	https://dx.doi.org/10.1016/j.urolonc.2023.11.004	No relevant population
DalMoro 2019	https://dx.doi.org/10.1007/s40520-018-0939-4	No relevant population
Davik 2022	https://dx.doi.org/10.1002/bco2.146	No relevant reference standard
Davik 2023	https://dx.doi.org/10.1111/bju.16163	No relevant reference standard

Day 2019	https://dx.doi.org/10.1177/2051415818773965	No relevant population
Deniffel 2021	https://doi.org/10.1148/radiol.2021204112	No relevant population
Deivasigamani 2023	https://dx.doi.org/10.1016/j.ejrad.2023.110929	No relevant population
DelMonte 2018	https://dx.doi.org/10.1007/s11547-017-0852-5	Excluded publication type
DelMonte 2018	https://dx.doi.org/10.1007/s11547-017-0825-8	No relevant population
DeNunzio 2021	https://dx.doi.org/10.1016/j.ejso.2021.04.033	No relevant population
de Oliveira Correia 2024	https://dx.doi.org/10.2214/AJR.23.30611	No relevant reference standard
Desai 2024	https://dx.doi.org/10.1101/2024.02.12.24302703	Excluded publication type
DeVulder 2023	https://dx.doi.org/10.1007/s00261-022-03745-5	No relevant population
Dhulaimi 2024	https://dx.doi.org/10.1186/s43055-024-01244-9	No relevant index test
Diamand 2024	https://dx.doi.org/10.1016/j.euf.2024.03.003	No relevant population
Diamand 2024	https://dx.doi.org/10.1007/s00345-024-05068-0	No relevant population
Dias 2023	https://dx.doi.org/10.5173/ceju.2023.198	No relevant reference standard
Dikaios 2019	https://dx.doi.org/10.1007/s00330-018-5799-y	No relevant population
Dixit 2023	http://impactfactor.org/PDF/IJPCR/15/IJPCR,Vol15,Issue3,Article150.pdf	No relevant population
Doan 2023	https://dx.doi.org/10.1111/bju.15929	No relevant population
Drost 2019	https://dx.doi.org/10.1002/14651858.CD012663.pub2	Superseded
Drost 2020	https://dx.doi.org/10.1016/j.eururo.2019.06.023	Overlapping data
Drudi 2019	https://dx.doi.org/10.21873/anticanres.13446	No relevant reference standard
Druskin 2018	https://dx.doi.org/10.1111/bju.14098	No relevant population
Dwivedi 2018	https://dx.doi.org/10.1002/jmri.25850	No relevant index test
Ecke 2021	https://dx.doi.org/10.1016/j.urolonc.2021.01.008	No relevant population
El-Achkar 2021	https://dx.doi.org/10.1080/2090598X.2021.1926727	No relevant reference standard
EL-Adalany 2021	https://dx.doi.org/10.1186/s43055-021-00443-y	No relevant reference standard
Eldred-Evans 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7456	No relevant index test
Eldred-Evans 2023	https://dx.doi.org/10.1111/bju.15899	No relevant reference standard
El-Khoury 2022	https://dx.doi.org/10.1177/20514158211004334	No relevant reference standard
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	No relevant population
Emmett 2022	https://dx.doi.org/10.2967/jnumed.121.263448	No relevant population
Emmett 2023	https://dx.doi.org/10.2967/jnumed.123.266164	No relevant population
Falagario 2020	https://dx.doi.org/10.1016/j.euo.2019.08.015	No relevant reference standard
Falagario 2021	https://dx.doi.org/10.5173/ceju.2021.3.074.R1	No relevant population
Falagario 2021	https://dx.doi.org/10.1016/j.euo.2020.08.014	No relevant reference standard
Falagario 2023	https://dx.doi.org/10.1007/s00345-023-04634-2	No relevant reference standard
Fang 2023	https://dx.doi.org/10.7717/peerj.16614	Excluded study design
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	No relevant reference standard
Feng 2024	https://dx.doi.org/10.2147/CMAR.S476636	No relevant reference standard
Feuer 2021	https://dx.doi.org/10.1097/JU.0000000000001406	No relevant reference standard
Fiorello 2022	https://dx.doi.org/10.1186/s43055-021-00653-4	No relevant reference standard
Fletcher 2023	https://dx.doi.org/10.1016/j.eururo.2022.12.007	No relevant population
Frantzi 2020	https://dx.doi.org/10.1080/23808993.2020.1804866	Excluded publication type
Fredsoe 2023	https://dx.doi.org/10.1016/j.euo.2023.07.006	No relevant population
Fu 2020	https://dx.doi.org/10.1089/end.2019.0902	No relevant reference standard
Gandaglia 2022	https://dx.doi.org/10.1016/j.euros.2021.06.016	Excluded publication type

Garcia-Reyes 2018	https://dx.doi.org/10.1016/j.juro.2017.09.075	No relevant reference standard
Gavin 2020	https://dx.doi.org/10.1016/j.euros.2020.07.001	No relevant population
Ge 2023	https://dx.doi.org/10.1002/cam4.6750	No relevant reference standard
Ghai 2022	https://dx.doi.org/10.1148/radiol.212163	No relevant reference standard
Girometti 2024	https://dx.doi.org/10.1007/s00261-024-04506-2	No relevant population
Glaser 2018	https://dx.doi.org/10.21037/tau.2018.03.21	Excluded publication type
Godtman 2024	https://doi.org/10.1016/j.euo.2023.11.003	No comparative data for outcome
Grey 2022	https://dx.doi.org/10.1016/S1470-2045(22)00016-X	No relevant reference standard
Gronberg 2018	https://dx.doi.org/10.1016/j.eururo.2018.06.022	No relevant reference standard
Gunzel 2021	https://dx.doi.org/10.1007/s00345-021-03699-1	No relevant population
Guo 2023	https://dx.doi.org/10.1186/s12894-023-01245-2	No relevant reference standard
Guo 2023	https://dx.doi.org/10.1038/s41391-023-00782-z	No relevant reference standard
Guo 2024	https://dx.doi.org/10.1097/RLU.0000000000004951	No relevant index test
Guo 2024	https://dx.doi.org/10.1186/s13244-024-01699-4	No relevant reference standard
Gupta 2021	https://dx.doi.org/10.4103/ijabmr.IJABMR_115_20	No relevant reference standard
Gurgitano 2020	https://dx.doi.org/10.23750/abm.v91i10-S.10251	Excluded publication type
Haack 2022	https://dx.doi.org/10.1007/s00345-022-04197-8	No relevant population
Hagens 2023	https://dx.doi.org/10.1007/s00345-022-04185-y	No relevant reference standard
Haider 2021	https://dx.doi.org/10.1016/j.clon.2021.07.016	No relevant reference standard
Haider 2022	https://dx.doi.org/10.5489/cuaj.7425	Excluded publication type
Haj-Mirzaian 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.4258	No relevant index test
Han 2020	https://dx.doi.org/10.1016/j.diii.2020.01.014	No relevant reference standard
Hansen 2020	https://dx.doi.org/10.1111/bju.14865	No relevant population
He 2019	https://dx.doi.org/10.3892/etm.2019.8151	No relevant population
He 2020	https://dx.doi.org/10.1245/s10434-019-08111-2	No relevant reference standard
Heetman 2020	https://dx.doi.org/10.23736/S0393-2249.20.03722-4	Excluded publication type
Hendriks 2021	https://dx.doi.org/10.1038/s41391-021-00367-8	No relevant reference standard
Henning 2019	https://dx.doi.org/10.1016/j.urology.2019.08.007	No relevant reference standard
Hepp 2022	https://dx.doi.org/10.1007/s00345-022-03991-8	No relevant population
Hoffman 2023	https://dx.doi.org/10.7326/J23-0017	Excluded publication type
Hoge 2020	https://dx.doi.org/10.1089/end.2020.0299	No relevant reference standard
Hruba 2024	https://dx.doi.org/10.1007/s11845-024-03771-w	No relevant population
Hsieh 2020	https://dx.doi.org/10.1007/s00345-019-02889-2	No relevant reference standard
Hsieh 2022	https://dx.doi.org/10.31083/j.jomh1806127	No relevant population
Huang 2023	https://dx.doi.org/10.4103/aja202218	No relevant reference standard
Huang 2024	https://dx.doi.org/10.4103/aja202412	No relevant reference standard
Hugosson 2022	https://dx.doi.org/10.1056/NEJMoa2209454	Excluded study design
Ippolito 2020	https://dx.doi.org/10.1111/iju.14316	No relevant reference standard
Ishioka 2018	https://dx.doi.org/10.1111/bju.14397	No relevant population
Isotani 2023	https://dx.doi.org/10.1016/j.prnil.2023.07.003	No relevant reference standard
Israel 2022	https://dx.doi.org/10.1111/bju.15562	No relevant reference standard
Jabbour 2023	https://dx.doi.org/10.1111/bju.16221	No relevant population
Jaderling 2024	https://dx.doi.org/10.1186/s12894-024-01553-1	No relevant index test
Jenifer 2024	https://dx.doi.org/10.36478/makrjms.2024.7.336.340	Full text unavailable

Josefsson 2024	https://dx.doi.org/10.1016/j.eururo.2024.04.037	No relevant reference standard
Kalapara 2022	https://dx.doi.org/10.1016/j.euo.2021.02.006	No relevant population
Kaneko 2023	https://dx.doi.org/10.1038/s41598-023-40371-7	No relevant reference standard
Karami 2023	https://dx.doi.org/10.5812/ijcm-132340	No relevant population
Kaufmann 2022	https://dx.doi.org/10.1002/pros.24286	No relevant population
Keck 2021	https://dx.doi.org/10.3390/cells10061315	No relevant reference standard
Kenigsberg 2023	https://dx.doi.org/10.1016/j.eururo.2023.02.022	Excluded publication type
Kim 2018	https://dx.doi.org/10.2214/AJR.17.18926	No relevant population
Kim 2020	https://dx.doi.org/10.1186/s12916-020-01548-3	No relevant reference standard
Kim 2020	https://dx.doi.org/10.1111/iju.14213	No relevant reference standard
Kim 2021	https://dx.doi.org/10.3390/medicina57050413	No relevant reference standard
Kim 2022	https://dx.doi.org/10.1097/JU.0000000000002168	No relevant population
Kim 2023	https://dx.doi.org/10.1016/j.urolonc.2021.08.006	Excluded publication type
Kizilay 2023	https://dx.doi.org/10.4274/uob.galenos.2023.2023.1.1	No relevant population
Kong 2023	https://dx.doi.org/10.1177/20514158211065946	No relevant reference standard
Kortenbach 2021	https://dx.doi.org/10.1016/j.heliyon.2021.e08325	No relevant index test
Kozel 2022	https://dx.doi.org/10.5489/cuaj.7472	No relevant reference standard
Kretschmer 2022	https://dx.doi.org/10.1038/s41598-022-08608-z	No relevant index test
Kwon 2023	https://dx.doi.org/10.1007/s11255-023-03674-2	No relevant index test
Laddha 2020	https://dx.doi.org/10.4103/iju.IJU_344_19	No relevant reference standard
Lahoti 2018	https://dx.doi.org/10.5114/pjr.2018.73292	No relevant reference standard
Lantz 2021	https://dx.doi.org/10.1007/s00345-020-03277-x	No relevant reference standard
Lazarovich 2021	https://dx.doi.org/10.5489/cuaj.6607	No relevant reference standard
Lazzeri 2022	https://dx.doi.org/10.3389/fonc.2022.968384	No relevant population
Lebastchi 2019	https://dx.doi.org/10.1038/s41585-019-0173-7	Excluded publication type
Lee 2021	https://dx.doi.org/10.1016/j.urolonc.2021.03.003	No relevant outcome
Lee 2021	https://dx.doi.org/10.1016/j.urolonc.2021.02.027	No relevant population
Lee 2021	https://dx.doi.org/10.1016/j.urology.2021.06.008	Excluded publication type
Lee 2022	https://dx.doi.org/10.1016/j.prnil.2021.08.003	No relevant population
Lee 2022	https://dx.doi.org/10.1259/bjr.20210509	Excluded publication type
Lee 2022	https://dx.doi.org/10.1097/CU9.0000000000000069	No relevant reference standard
Lei 2022	https://dx.doi.org/10.3389/fonc.2022.992032	No relevant reference standard
Lenfant 2022	https://dx.doi.org/10.1007/s00345-022-04013-3	No relevant reference standard
Li 2023	https://dx.doi.org/10.1002/jmri.28505	Excluded study design
Li 2023	https://dx.doi.org/10.1007/s00432-023-05008-2	No relevant reference standard
Li 2024	https://dx.doi.org/10.62347/JHYY2053	No relevant population
Liu 2018	https://dx.doi.org/10.4103/aja.aja_19_18	No relevant reference standard
Liu 2020	https://dx.doi.org/10.1038/s41598-020-62015-w	No relevant reference standard
Liu 2021	https://dx.doi.org/10.3389/fonc.2021.732027	No relevant reference standard
Liu 2022	https://dx.doi.org/10.1259/bjr.20220209	No relevant reference standard
Liu 2024	https://dx.doi.org/10.1007/s11547-024-01758-2	No relevant population
Lockhart 2022	https://dx.doi.org/10.1177/20514158221085081	No relevant reference standard
Lombardo 2021	https://dx.doi.org/10.1080/1354750X.2020.1841294	No relevant reference standard
Lopez 2021	https://dx.doi.org/10.1111/bju.15337	No relevant population

Lophatananon 2023	https://dx.doi.org/10.1177/20514158211059057	No relevant reference standard
Lu 2019	https://dx.doi.org/10.1186/s40644-019-0208-6	No relevant reference standard
Lv 2023	https://dx.doi.org/10.1590/S1677-5538.IBJU.2023.0060	No relevant population
Maggi 2021	https://dx.doi.org/10.3390/cancers13092047	No relevant reference standard
Mahajan 2022	https://dx.doi.org/10.4103/jcrt.JCRT_1313_20	No relevant reference standard
Majchrzak 2021	https://dx.doi.org/10.5173/ceju.2021.3.R2.0111	No relevant reference standard
Malshy 2024	https://dx.doi.org/10.1002/pros.24757	No relevant reference standard
Manfredi 2021	https://dx.doi.org/10.23736/S2724-6051.21.04341-1	Excluded publication type
Mathur 2019	https://dx.doi.org/10.1007/s00261-018-1696-8	No relevant population
Mazzetti 2024	https://dx.doi.org/10.1007/s00330-023-10542-1	No relevant reference standard
Merriel 2020	https://dx.doi.org/10.1016/j.jacr.2019.08.031	No relevant outcome
Messina 2023	https://dx.doi.org/10.1007/s00330-023-09605-0	No relevant reference standard
Meza 2022	https://dx.doi.org/10.1186/s12894-022-01066-9	No relevant reference standard
Miah 2020	https://dx.doi.org/10.1016/j.euo.2019.03.005	No relevant population
Mian 2024	https://dx.doi.org/10.1097/JU.0000000000003979	Excluded study design
Mo 2022	https://dx.doi.org/10.3389/fonc.2022.1068893	No relevant reference standard
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	No relevant population
Moore 2018	https://dx.doi.org/10.1016/j.eururo.2018.03.042	Excluded publication type
Moraes 2020	https://dx.doi.org/10.1007/s00345-019-02827-2	No relevant reference standard
Morote 2022	https://dx.doi.org/10.1177/03936155221081537	No relevant reference standard
Morote 2022	https://dx.doi.org/10.3390/cancers14061589	No relevant reference standard
Morote 2023	https://dx.doi.org/10.1111/bju.15998	No relevant reference standard
Morote 2023	https://dx.doi.org/10.1016/j.urolonc.2023.05.003	No relevant reference standard
Morote 2023	https://dx.doi.org/10.1016/j.euros.2023.03.013	No relevant reference standard
Morote 2024	https://dx.doi.org/10.3390/jpm14020130	No relevant reference standard
Morote 2024	https://dx.doi.org/10.1016/j.urolonc.2023.09.020	No relevant reference standard
Morote 2024	https://dx.doi.org/10.3390/biom14020193	No relevant reference standard
Morote 2024	https://dx.doi.org/10.3390/cancers16132306	No relevant population
Mortezavi 2021	https://dx.doi.org/10.1016/j.euf.2020.05.002	No relevant reference standard
Mussi 2018	https://dx.doi.org/10.1590/S1677-5538.IBJU.2018.0102	No relevant reference standard
Naik 2022	https://dx.doi.org/10.1016/j.jacr.2022.08.013	No relevant population
Nassiri 2019	https://dx.doi.org/10.1590/S1677-5538.IBJU.2018.0886	Excluded publication type
Nepal 2020	https://dx.doi.org/10.5152/tud.2020.20248	No relevant reference standard
Niu 2018	https://dx.doi.org/10.2214/AJR.17.18494	No relevant reference standard
Niu 2018	https://dx.doi.org/10.2214/AJR.17.18946	No relevant index test
Nowier 2022	https://dx.doi.org/10.1080/2090598X.2022.2067615	No relevant reference standard
Obino 2022	https://dx.doi.org/10.4314/aas.v19i2.8	No relevant reference standard
Oh 2020	https://dx.doi.org/10.4111/icu.2020.61.1.28	No relevant outcome
Okabe 2022	https://dx.doi.org/10.1016/j.urology.2022.07.030	No relevant reference standard
Okubo 2022	https://dx.doi.org/10.1016/j.prp.2022.154188	No relevant reference standard
Onder 2023	https://dx.doi.org/10.4274/dir.2023.232414	No relevant reference standard
Orecchia 2024	https://dx.doi.org/10.1007/s00345-024-04772-1	No relevant outcome
Ortner 2024	https://dx.doi.org/10.3390/jcm13051355	No relevant reference standard
Pagniez 2020	https://dx.doi.org/10.1097/JU.0000000000000757	Superseded

Palsdottir 2023	https://dx.doi.org/10.1016/j.euf.2022.11.021	No relevant reference standard
Pan 2022	https://dx.doi.org/10.3389/fsurg.2022.1096387	No relevant reference standard
Pantelidou 2022	https://dx.doi.org/10.1371/journal.pone.0274014	No relevant reference standard
Parekh 2022	https://dx.doi.org/10.1016/j.euros.2022.04.017	No relevant reference standard
Park 2020	https://dx.doi.org/10.1007/s00261-020-02667-4	No relevant reference standard
Park 2020	https://dx.doi.org/10.1097/JU.0000000000001306	No relevant population
Patel 2019	https://dx.doi.org/10.1007/s00261-018-1751-5	No relevant reference standard
Patel 2020	https://dx.doi.org/10.21037/tau.2020.01.33	No relevant population
Patel 2022	https://dx.doi.org/10.1002/cncr.33875	No relevant reference standard
Patel 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.1516	No relevant outcome
Pellegrino 2023	https://dx.doi.org/10.1016/j.euf.2022.10.002	Excluded study design
Pepe 2022	https://dx.doi.org/10.4081/aiua.2022.3.274	No relevant reference standard
Pepe 2023	https://dx.doi.org/10.1016/j.clgc.2023.06.007	No relevant reference standard
Pereira-Azevedo 2018	https://dx.doi.org/10.21037/tau.2017.12.21	No relevant reference standard
Pham 2024	https://dx.doi.org/10.1002/cnr2.1962	No relevant reference standard
Pickersgill 2019	https://dx.doi.org/10.1016/j.urology.2019.01.035	No relevant reference standard
Popita 2018	https://pubmed.ncbi.nlm.nih.gov/30358212/	No relevant reference standard
Porzycki 2019	https://dx.doi.org/10.5114/jcb.2019.90085	No relevant reference standard
Punnen 2018	https://dx.doi.org/10.1371/journal.pone.0201384	No relevant reference standard
Pye 2021	https://dx.doi.org/10.3390/cancers13081985	No relevant reference standard
Pylvalainen 2024	https://dx.doi.org/10.1158/1055-9965.EPI-23-1208	No relevant reference standard
Qiu 2022	https://dx.doi.org/10.1007/s00259-021-05636-1	No relevant reference standard
Radtke 2019	https://dx.doi.org/10.1371/journal.pone.0221350	No comparative data for outcome
Radtke 2020	https://dx.doi.org/10.1016/j.eururo.2020.04.014	Excluded publication type
Rajendran 2024	https://dx.doi.org/10.1093/bjr/tqad027	No relevant reference standard
Ramacciotti 2024	https://dx.doi.org/10.1590/S1677-5538.IBJU.2024.0354	No relevant reference standard
Raman 2021	https://dx.doi.org/10.1097/JU.0000000000001832	No relevant population
Regis 2019	https://dx.doi.org/10.1080/21681805.2018.1551243	No relevant population
Reijnen 2021	https://dx.doi.org/10.1007/s00261-021-03249-8	No relevant reference standard
Reijnen 2023	https://dx.doi.org/10.3389/fonc.2023.1102860	No relevant reference standard
Rembak-Szynkiewicz 2022	https://dx.doi.org/10.5603/EP.a2022.0042	No relevant population
Remmers 2022	https://dx.doi.org/10.1016/j.euros.2021.11.002	No relevant reference standard
Ren 2022	https://dx.doi.org/10.3389/fonc.2022.1038177	No relevant reference standard
Ren 2024	https://dx.doi.org/10.3389/fonc.2024.1413953	No relevant reference standard
Rico 2020	https://dx.doi.org/10.5152/tud.2020.20111	No relevant population
RodriguezSanchez 2020	https://dx.doi.org/10.1016/j.eururo.2020.04.022	Excluded publication type
Rosario 2019	https://dx.doi.org/10.1016/j.eururo.2018.12.001	Excluded publication type
Roumiguie 2020	https://dx.doi.org/10.3390/cancers12020285	No relevant population
Rozas 2019	https://dx.doi.org/10.1590/S1677-5538.IBJU.2018.0564	No relevant population
Ryoo 2020	https://dx.doi.org/10.1016/j.prnil.2020.03.003	No relevant reference standard
Saba 2020	https://dx.doi.org/10.1097/JU.0000000000000622	No relevant population
Sahin 2024	https://dx.doi.org/10.1016/j.prnil.2024.06.001	No relevant reference standard
Sakhaei 2024	https://dx.doi.org/10.18502/fbt.v11i2.15334	No relevant population
Samora 2023	https://dx.doi.org/10.1016/j.ucl.2022.09.008	Excluded publication type

Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	No relevant population
Sathianathen 2020	https://dx.doi.org/10.1016/j.eururo.2020.03.048	No relevant population
Sauck 2022	https://dx.doi.org/10.3390/tomography8040169	No relevant population
Schelb 2019	https://dx.doi.org/10.1148/radiol.2019190938	No relevant population
Schieda 2024	https://dx.doi.org/10.1148/radiol.231383	No relevant population
Schmid 2023	https://dx.doi.org/10.1002/pros.24435	No relevant population
Schneider 2019	https://dx.doi.org/10.1016/j.ejrad.2019.108660	No relevant population
Schoots 2021	https://doi.org/10.1111/bju.15277	Superseded
Schoots 2020	https://dx.doi.org/10.1016/j.euo.2019.10.001	No relevant reference standard
Schrader 2024	https://dx.doi.org/10.1007/s00330-024-10818-0	No relevant population
Segal 2020	https://dx.doi.org/10.1016/j.annonc.2020.06.025	No relevant reference standard
Seref 2022	https://dx.doi.org/10.1002/pros.24255	No relevant population
Setia 2022	https://dx.doi.org/10.1016/j.urolonc.2021.08.029	No relevant population
Sharqawi 2023	https://dx.doi.org/10.1186/s12894-023-01241-6	No relevant population
Siddiqui 2023	https://dx.doi.org/10.1038/s41391-023-00660-8	No relevant reference standard
Sigle 2022	https://dx.doi.org/10.3390/cancers14215230	No relevant population
Singla 2023	https://dx.doi.org/10.4103/jcrt.jcrt_280_22	No relevant reference standard
Sivaraman 2022	https://dx.doi.org/10.4103/iju.iju_222_21	No relevant reference standard
Sokhi 2020	https://dx.doi.org/10.1016/j.crad.2020.08.011	No relevant reference standard
Sokhi 2022	https://dx.doi.org/10.1016/j.crad.2022.03.004	No relevant reference standard
Song 2023	https://dx.doi.org/10.1007/s00261-022-03750-8	No relevant reference standard
Sonn 2019	https://dx.doi.org/10.1016/j.euf.2017.11.010	No relevant population
Sountoulides 2021	https://dx.doi.org/10.1097/JU.0000000000001639	No relevant index test
Stabile 2018	https://dx.doi.org/10.1016/j.euo.2018.01.002	No relevant reference standard
Stavrinides 2023	https://dx.doi.org/10.1016/j.euf.2023.03.011	No relevant population
Stephan 2021	https://dx.doi.org/10.1007/s00345-020-03585-2	Excluded study design
Stevens 2020	https://dx.doi.org/10.1016/j.urolonc.2020.05.024	No relevant reference standard
Stevens 2023	https://dx.doi.org/10.1177/02841851231187135	No relevant reference standard
Stone 2021	https://dx.doi.org/10.1002/bco2.111	No relevant population
Stonier 2021	https://dx.doi.org/10.1016/j.euf.2020.09.012	No relevant reference standard
Stovsky 2019	https://dx.doi.org/10.1097/JU.0000000000000185	No relevant index test
Su 2022	https://dx.doi.org/10.3389/fonc.2022.957892	No relevant reference standard
Sun 2023	https://dx.doi.org/10.1016/j.eclinm.2023.102027	No relevant reference standard
Tafuri 2020	https://dx.doi.org/10.1007/s00345-019-02835-2	No relevant reference standard
Takeshima 2020	https://dx.doi.org/10.1007/s11255-020-02533-8	No relevant reference standard
Taneja 2019	https://dx.doi.org/10.1097/01.JU.0000557757.85458.f2	Excluded publication type
Taneja 2020	https://dx.doi.org/10.1097/JU.0000000000001283.02	Excluded publication type
Tao 2021	https://dx.doi.org/10.3389/fonc.2021.811866	No relevant reference standard
Tay 2021	https://dx.doi.org/10.1002/bco2.99	No relevant population
Teixeira Anacleto 2022	https://dx.doi.org/10.4081/aiua.2022.1.32	No relevant reference standard
Tezcan 2023	https://dx.doi.org/10.5152/tud.2023.220199	No relevant reference standard
Thaiss 2022	https://dx.doi.org/10.1007/s00345-022-04120-1	No relevant reference standard
Tosoian 2022	https://dx.doi.org/10.1016/j.urology.2021.11.033	No relevant reference standard
Tosun 2021	https://dx.doi.org/10.1016/j.clinimag.2021.03.011	No relevant reference standard

Triquell 2022	https://dx.doi.org/10.3390/cancers14194747	Excluded study design
Tsai 2020	https://dx.doi.org/10.1111/1754-9485.13029	No relevant reference standard
Tully 2021	https://dx.doi.org/10.1016/j.euf.2020.09.014	No relevant reference standard
van der Leest 2019	https://dx.doi.org/10.1016/j.eururo.2019.05.029	No relevant reference standard
van der Leest 2019	https://dx.doi.org/10.1016/j.eururo.2018.11.023	No relevant reference standard
Verma 2020	https://dx.doi.org/10.1080/13685538.2021.1873263	No relevant reference standard
Vigneswaran 2021	https://dx.doi.org/10.1038/s41391-020-00297-x	No relevant reference standard
Vinje 2023	https://dx.doi.org/10.1016/j.euf.2023.08.009	No relevant population
Wagaskar 2022	https://dx.doi.org/10.22037/uj.v18i.6852	No relevant reference standard
Wang 2019	https://dx.doi.org/10.1016/j.urolonc.2019.05.002	No relevant reference standard
Wang 2020	https://dx.doi.org/10.1007/s00261-019-02281-z	No relevant reference standard
Wang 2021	https://dx.doi.org/10.1016/j.urolonc.2021.06.004	No relevant population
Wang 2021	https://dx.doi.org/10.4103/jmu.jmu_96_21	Excluded publication type
Wang 2022	https://dx.doi.org/10.3389/fonc.2022.1024204	No relevant reference standard
Wang 2023	https://dx.doi.org/10.1007/s11255-023-03631-z	No relevant reference standard
Wang 2024	https://dx.doi.org/10.21037/qims-23-875	No relevant reference standard
Wei 2022	https://dx.doi.org/10.1007/s00261-022-03592-4	No relevant reference standard
Weiser 2023	https://dx.doi.org/10.1002/jmri.28891	No relevant population
Wen 2022	https://dx.doi.org/10.3389/fonc.2022.861928	No relevant reference standard
Wenzel 2021	https://dx.doi.org/10.3389/fsurg.2021.633196	No relevant population
Westhoff 2019	https://dx.doi.org/10.1016/j.urolonc.2019.07.004	No relevant reference standard
Westphalen 2019	https://dx.doi.org/10.1590/S1677-5538.IBJU.2018.0768	No relevant population
Wetterauer 2021	https://dx.doi.org/10.1038/s41598-021-99854-0	No relevant population
Wibulpolprasert 2022	https://dx.doi.org/10.35755/jmedassocthai.2022.03.13284	No relevant population
Wiemer 2021	https://dx.doi.org/10.1016/j.euf.2020.06.022	No relevant reference standard
Wong 2024	https://dx.doi.org/10.1016/j.euo.2024.01.002	No relevant reference standard
Wroclawski 2020	https://dx.doi.org/10.1007/s00261-020-02411-y	No relevant population
Wu 2023	https://dx.doi.org/10.1007/s11255-023-03705-y	Excluded study design
Wu 2024	https://dx.doi.org/10.1038/s41391-023-00729-4	No relevant population
Wysock 2020	https://dx.doi.org/10.1016/j.urology.2020.02.032	No relevant reference standard
Xiang 2019	https://dx.doi.org/10.1007/s00330-019-06274-w	No relevant reference standard
Xu 2019	https://dx.doi.org/10.1186/s40644-019-0274-9	No relevant reference standard
Xu 2020	https://dx.doi.org/10.1007/s00261-020-02738-6	No relevant reference standard
Xu 2021	https://dx.doi.org/10.1080/03007995.2021.1949270	No relevant reference standard
Xu 2023	https://dx.doi.org/10.1097/CU9.0000000000000116	No relevant reference standard
Yanez-Castillo 2023	https://dx.doi.org/10.1007/s00432-023-04860-6	No relevant reference standard
Ye 2022	https://dx.doi.org/10.4111/icu.20220056	No relevant reference standard
Ye 2024	https://dx.doi.org/10.1016/j.euros.2024.04.001	No relevant population
Yilmaz 2023	https://dx.doi.org/10.1148/radiol.221309	No relevant reference standard
Yin 2021	https://dx.doi.org/10.1177/15330338211019418	No relevant reference standard
Ying 2023	https://dx.doi.org/10.21037/tau-23-371	No relevant population
Yokoo 2019	https://dx.doi.org/10.1177/0391560319858482	No relevant reference standard
Yu 2021	https://dx.doi.org/10.1186/s12894-021-00849-w	No relevant reference standard
Zalesky 2019	https://dx.doi.org/10.1159/000500350	No relevant reference standard

Zalesky 2020	https://dx.doi.org/10.5507/bp.2019.050	No relevant reference standard
Zattoni 2024	https://dx.doi.org/10.1016/j.euros.2024.05.009	Excluded study design
Zawaideh 2020	https://dx.doi.org/10.1007/s00330-020-06782-0	No relevant reference standard
Zawaideh 2020	https://dx.doi.org/10.1259/bjr.20200298	No relevant reference standard
Zhang 2018	https://dx.doi.org/10.1186/s12957-018-1367-9	No relevant outcome
Zhang 2019	https://dx.doi.org/10.1002/jum.14878	No relevant reference standard
Zhang 2020	https://dx.doi.org/10.1007/s10147-019-01524-9	No relevant population
Zhang 2022	https://dx.doi.org/10.1007/s00261-022-03553-x	No relevant reference standard
Zhang 2023	https://dx.doi.org/10.4103/aja202288	No relevant reference standard
Zhang 2024	https://dx.doi.org/10.1002/pros.24669	No relevant reference standard
Zhou 2022	https://dx.doi.org/10.1002/pros.24302	No relevant reference standard
Zhou 2022	https://dx.doi.org/10.1186/s13550-022-00881-3	No relevant reference standard
Zhou 2023	https://dx.doi.org/10.3390/jcm12010339	No relevant reference standard
Zhu 2023	https://dx.doi.org/10.1177/15579883231161292	No relevant reference standard
Articles from Drost 2019 systematic review		
Abd-Alazeez 2014	https://doi.org/10.1016%2Fj.urolonc.2013.06.007	No relevant population
Dal Moro 2019	https://doi.org/10.1007/s40520-018-0939-4	No relevant population
Distler 2017	https://doi.org/10.1016/j.juro.2017.03.130	No relevant population
Grey 2015	https://doi.org/10.1111/bju.12862	No relevant index test
Hansen 2016	https://doi.org/10.1016/j.eururo.2016.02.064	Overlapping data
Hansen 2017	https://doi.org/10.1111/bju.14049	No relevant population
Kesch 2017	https://doi.org/10.1159/000458764	No relevant population
Lawrence 2014	https://doi.org/10.1007/s00330-014-3159-0	No relevant population
Muthuveloe 2016	https://doi.org/10.5173/ceju.2016.675	No relevant index test
Nafie 2014	https://doi.org/10.1038/pcan.2014.4	No relevant index test
Nafie 2017	https://pubmed.ncbi.nlm.nih.gov/28299763/	No relevant population
Pepe 2013	https://pubmed.ncbi.nlm.nih.gov/23482802/	No relevant population
Ploussard 2014	https://doi.org/10.1016/j.eururo.2012.05.049	No relevant index test
Thompson 2016	https://doi.org/10.1016/j.juro.2015.10.140	No relevant reference standard
Tsivian 2017	https://doi.org/10.1111/iju.13251	No relevant population

3.8 Clinical question 7 – mpMRI PICO 7B

Clinical question: *Can/should we use multiparametric MRI to triage men with no history of prostate cancer and an elevated PSA for biopsy?*

Systematic review report for PICO 7B: Randomised controlled trials of multiparametric MRI triage for biopsy naïve men with elevated PSA levels

Authors

Denise Campbell, Susan Yuill, Suzanne Hughes

PICOs

This systematic review addresses the following PICOs which are summarised in detail in Table 1.

PICO 7Ba: *"For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, how does multiparametric MRI triage for biopsy compare with all individuals undergoing biopsy for the outcomes of all-cause mortality, prostate cancer mortality, metastatic disease and the detection of clinically significant cancer in randomised controlled trials?*

PICO 7Bb: *"For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, and who are multiparametric MRI negative and do not undergo biopsy how do different follow-up protocols compare for the outcomes of all-cause mortality, prostate cancer mortality and metastatic disease?"*

Table 1. *PICO components*

Population	***Intervention***	***Comparator***	***Outcomes#***	***Study design***
PICO 7Ba				
Individuals with a prostate and no history of prostate cancer and elevated PSA levels who are biopsy naïve	mpMRI triage for biopsy: mpMRI PIRADS* ≥ 3 or ≥ 4 with targeted biopsy +/- template/systematic biopsy if mpMRI-positive	No mpMRI triage: All individuals undergo biopsy – systematic biopsy of at least 12 cores for all	All-cause mortality Prostate cancer mortality Metastases	RCTs or systematic reviews thereof
		No mpMRI triage: All individuals undergo biopsy – systematic biopsy of at least 20** cores for all	Outcomes that can be addressed by diagnostic accuracy studies: ISUP grade ≥ 2 prostate cancer detection ISUP grade 1 prostate cancer detection Biopsy rates	
PICO 7Bb				
Individuals with a prostate and no history of prostate cancer and elevated PSA levels with a negative mpMRI who have not undergone biopsy	Follow-up protocol	Another follow-up protocol or no specific follow-up	All-cause mortality Prostate cancer mortality Metastases	RCTs or systematic reviews thereof

ISUP = International Society of Urological Pathology; mpMRI = multiparametric MRI; PIRADS = Prostate Imaging Reporting and Data System; RCTs = randomised controlled trials
** Or Likert 1-5 scale*
*** Restricted to RCTs in which the comparator is ≥20-core systematic biopsy as per current Australian practice*
 # Overall or by age, PSA level or risk

1. Methods

1.1 Selection criteria

Table 2a. *Selection criteria for systematic review of randomised controlled trials comparing mpMRI triage for biopsy vs no mpMRI triage for biopsy-naïve men*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	Diagnostic accuracy studies
Study design	Randomised controlled trials or systematic reviews thereof	Cohort studies
Population	Individuals with a prostate with a clinical suspicion of prostate cancer due to elevated PSA levels or abnormal DRE who are biopsy naïve including age, PSA level or risk level restricted sub-groups.	Clinical suspicion based on positive DRE only (not based on PSA test). Patients have had a prior negative biopsy > 10% of population have undergone prior biopsy and outcomes not stratified for biopsy-naïve patients. Individuals with prior prostate cancer diagnosis.
Intervention	**mpMRI triage** • only mpMRI-positive men undergo biopsy (targeted +/- systematic biopsy) • mpMRI threshold for biopsy is a score of ≥3 or ≥4 on PIRADS v1 or v2 or v2.1 or a 5-point Likert scale	Biparametric MRI MpMRI includes MRS and results not available for mpMRI (T1WI + T2WI + DWI + DCE) alone Likert scale < 5 points mpMRI threshold unclear or not reported
Comparator	**No triage** All participants undergo systematic biopsy • Transperineal or transrectal • ≥ 20 cores for cancer detection outcomes • ≥ 12 cores for mortality and metastases outcomes	Radical prostatectomy specimen (restricted to patients with prostate cancer diagnosis)
Outcome	Cancer detection outcomes: ISUP grade ≥ 2 (primary outcome), or ISUP grade ≥ 3, or ISUP grade 1 Prostate cancer-specific mortality Overall mortality Metastases Overall or by age, PSA level or risk subgroups	ISUP grade ≥ 2 or a subgroup of ISUP grade 1 for example • Max CCL ≥5 mm for Gleason score 6 disease • Max CCL ≥5 mm.
Publication date	From 1st January 2010	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

CCL = cancer core length; DCE = dynamic contrast enhancement; DWI = diffusion weighted index; ISUP = International Society of Urological Pathology; mpMRI = multiparametric MRI; MRS = magnetic resonance spectroscopy; PIRADS = Prostate Imaging Reporting and Data System; T1WI and T2WI = T1 and T2 weighted images

Table 2b. *Selection criteria for systematic review of randomised controlled trials comparing mpMRI triage for biopsy vs no mpMRI triage for biopsy-naïve men*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	Diagnostic accuracy studies
Study design	Randomised controlled trials or systematic reviews thereof	Cohort studies
Population	Biopsy naïve individuals with elevated PSA levels or abnormal DRE who are mpMRI negative (mpMRI score < 3 or <4) and have not undergone a biopsy	Clinical suspicion based on positive DRE only (not based on PSA test). Patients are biparametric MRI negative Patients who have had a prior negative biopsy > 10% of population have undergone prior biopsy and outcomes not stratified for biopsy-naïve patients. Individuals with prior prostate cancer diagnosis.
Intervention	Follow-up protocol	
Comparator	Another follow-up protocol Or no specific follow-up	
Outcome	Prostate cancer-specific mortality Overall mortality Metastases	
Publication date	From 1st January 2010	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

DRE = digital rectal examination; mpMRI = multiparametric MRI

1.2 Definitions and terminology

For the purposes of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).

ISUP grade ≥ 3 prostate cancer is prostate cancer scored as Gleason Score 7(4+3) or higher on histopathological findings (Epstein 2016).

ISUP grade 1 prostate cancer is prostate cancer scored as Gleason Score 6(3+3) on histopathological findings (Epstein 2016).

Multi-parametric MRI (mpMRI) refers to an imaging protocol used to detect and characterise tissue abnormalities to determine the presence and severity of cancer. Prostate mpMRI acquisition includes T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging.

Systematic biopsy includes template and saturation biopsies.

Targeted biopsy refers to a multiparametric MRI-targeted biopsy using cognitive, software registration or in-bore image fusion techniques to identify target/s.

- Cognitive image fusion refers to the operator visually fusing MRI images and real time ultrasound pictures.
- Software registration image fusion refers to using software to fuse uploaded MRI images to real time ultrasound.
- In-bore image fusion refers to fusing prior MRI images and a real time MRI during biopsy.

1.3 Guidelines searches

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website

- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, as the evidence for mpMRI triage continues to evolve, be based on literature published up until 2022 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations), Embase and Cochrane CENTRAL databases were searched on 5th December 2023 combining text words and database-specific subject headings for prostate cancer, multiparametric MRI and biopsy, and a filter for randomised controlled trials (RCT / CCT - MEDLINE, Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 2023-11-30.)

Searches were limited to articles published in English from 1st January 2010 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st September 2024. The searches were designed to identify potentially relevant trials in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the search is included as Appendix A. Potentially relevant systematic reviews identified by a search for systematic reviews of multiparametric MRI for the detection of prostate cancer undertaken for PICO 7A were also assessed for inclusion. Reference lists of recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

Extraction of study characteristics and results were planned. The following study characteristics were to be extracted: Country and year of publication, participant eligibility and age, duration of follow-up, components of intervention arm, components of comparator arm, relevant outcomes reported, subgroup data available, and additional information including notable study limitations. The following effect estimates were to be extracted: effect estimates and 95% confidence intervals as reported in the study or calculated using relevant reported data. Pooled analyses were planned where there were two or more studies reporting the same outcome at corresponding time points.

1.6 Risk of bias assessments

Independent assessments of the risk of bias by two reviewers using Cochrane Collaboration Risk of Bias-II tool (Sterne 2019) were planned.

1.7 GRADE assessment of the certainty of the evidence

GRADE assessments were planned to assess the certainty of the body of evidence for each outcome. (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence would be rated high, moderate, low or very low based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Schunemann 2013) and Schunemann et al 2022. As per GRADE guidance, randomised controlled trials started with a high level of certainty in the evidence and were to be downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were serious concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

1.8 Ongoing trials searches

Potentially relevant ongoing trials were identified from literature and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing randomised controlled trials registered or posted by 26 June 2024. The clinical trial registries were searched with the search terms listed below:

Clinicaltrials.gov using the terms:

"prostate cancer" and "multiparametric MRI" and "systematic biopsy"

"prostate cancer" and "magnetic resonance imaging" and "TRUS biopsy"

"prostate cancer" and "magnetic resonance imaging" and "transperineal biopsy"

"prostate cancer" and "multiparametric MRI" and "biopsy"

International Clinical Trials Registry Platform using the terms:

"biopsy" and "prostate cancer" and "MRI"

"prostate cancer" and "magnetic resonance imaging"

"prostate cancer" and "multiparametric MRI"

"prostate cancer" and "systematic biopsy"

"prostate cancer" and "screening"

Australia and New Zealand Clinical Trial Registry using the terms:

"multiparametric MRI" and "early detection/screening" or "diagnosis/prognosis" and "prostate cancer"

2. Results

2.1 Guidelines searches

One potentially relevant guideline was identified which was based on systematic reviews of the literature published up until 2022 or later. It was not considered for adoption as it did not directly consider using mpMRI alone to triage men with elevated PSA levels to biopsy (Appendix B).

2.2 Literature searches

Figure 1 outlines the process for identifying relevant articles published from 2010 onwards. The combined search of Medline, Embase and CENTRAL databases retrieved 2161 unique records which were assessed by one reviewer, of which 28 articles were retrieved for a more detailed evaluation by two reviewers. An

additional nine potentially relevant systematic reviews identified by a search for systematic reviews of multiparametric MRI detection of prostate cancer undertaken for PICO 7A were also retrieved and assessed for inclusion.

There were no RCTs or systematic reviews that met the inclusion criteria for either PICO. There were no studies that included Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.

The retrieved articles that were not included in this update and the reasons for their exclusion are documented in Appendix C. The main reasons for exclusion were no outcome of interest, ineligible study design, or systematic review that did not have the same inclusion criteria as this systematic review.

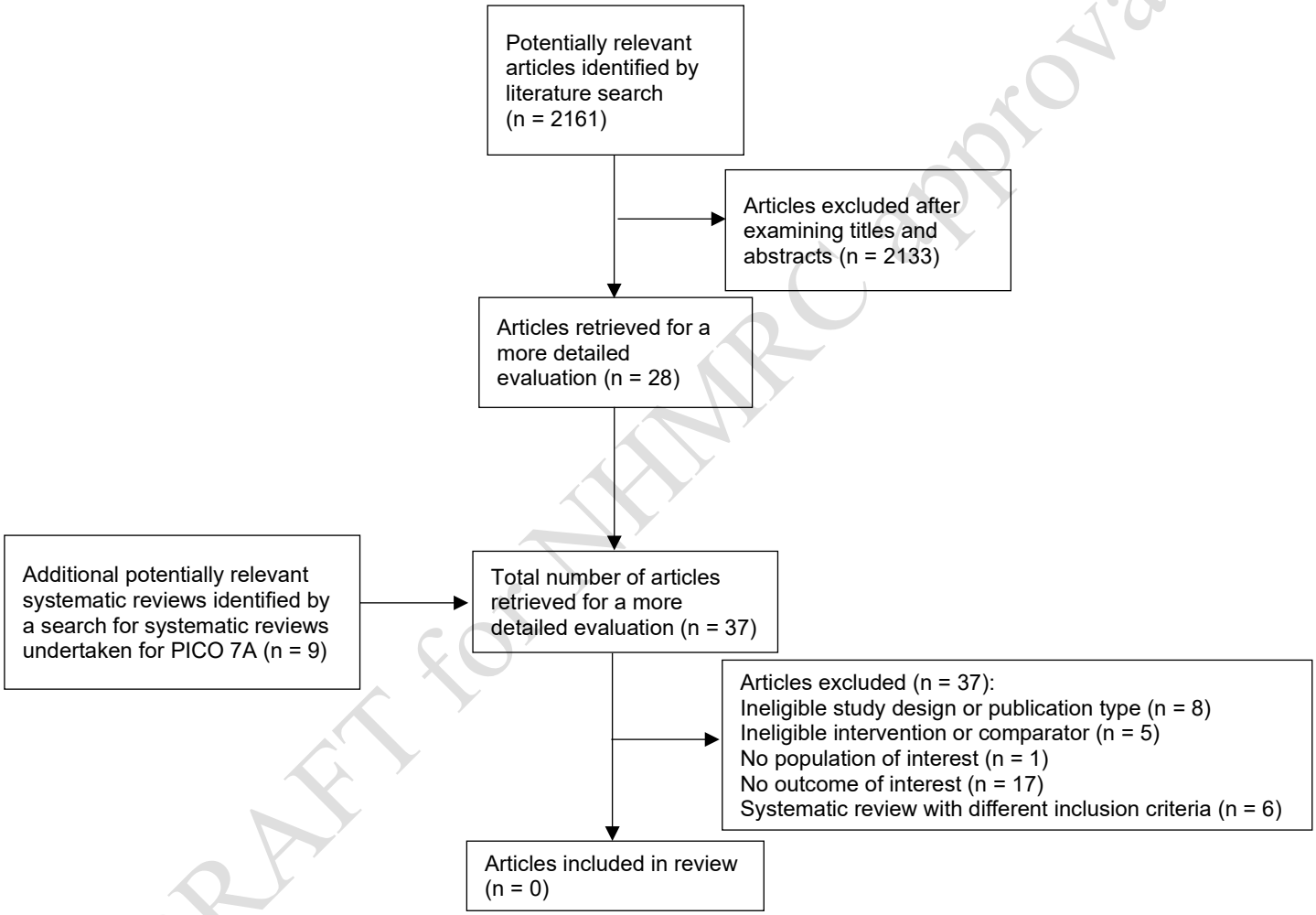

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

3. Ongoing clinical trials

Three ongoing trial protocols potentially addressing PICO 7Ba were identified by clinical trial registry and literature searches.

Table 3. *Summary of potentially relevant ongoing randomised controlled trials comparing mpMRI triage for biopsy with no mpMRI triage for biopsy naïve individuals*

Study ID Publications	***Study name, location and study design***	***Start date***	***Planned completion date***	***Population***	***Intervention***	***Comparator***	***Outcomes***
ISRCTN94604465 Kohestani 2021	Goteborg Prostate Cancer Screening 2 Trial Sweden (Goteborg-2) RCT – 4 arms	2015	2040	Men aged 50-60 years	PSA testing – frequency and age to cease dependent on previous PSA level. MpMRI for initial screen and biparametric MRI for subsequent screens Arm 1: If PSA level ≥ 3 ng/ml, **no MRI triage** MRI followed by systematic biopsy (10-12 core) regardless of MRI results +/- targeted biopsy Arm 2: If PSA level ≥ 3 ng/ml, **MRI triage** If PIRADS 3-4 targeted biopsy. If PIRADS 5 standard biopsy + targeted biopsy If PIRADS 1-2 no biopsy unless PSA ≥ 10.0 ng/mL Arm 3: If PSA level ≥ 1.8 ng/ml**, MRI triage** If PIRADS 3-4 targeted biopsy. If PIRADS 5 standard biopsy + targeted biopsy If PIRADS 1-2 no biopsy unless PSA ≥ 10.0 ng/mL	Usual care	*Primary* Clinically insignificant cancer (Gleason score 3+3) *Secondary* Clinically significant cancer (Gleason score ≥ 3+4) Prostate cancer mortality for screened vs no screened at 12 years and then every 3 years
NCT04685928	Extended Systematic Versus MRI-Assisted Prostate Transperineal Biopsy (SMART)	2021	2025	Biopsy naïve men aged ≥18 years with PSA 4-20 ng/ml +/- DRE ≤ cT2.	**mpMRI triage** mpMRI using PIRADS v2.1 If PIRADS ≥ 3 MRI-targeted biopsy (3-4 cores) plus12-core systematic transperineal biopsy (sparing MRI-target). If PIRADS < 3 no biopsy	24-core systematic transperineal biopsy	*Primary* ISUP grade ≥ 2 prostate cancer *Secondary* ISUP grade 1 prostate cancer Biopsies avoided 30-day post-biopsy adverse events Cancer core length of most involved biopsy core Health-related quality of life Costs
NCT05154162 Buteau 2024	PSMA PET Additive Value for Prostate Cancer Diagnosis in	2022	2028	Biopsy naïve men aged ≥18 years with a clinical suspicion of	**mpMRI and PSMA PET/CT triage** **Pelvic** PSMA PET/CT reviewed using the PRIMARY score.	Template transperineal prostate biopsies.	*Primary* Clinically significant prostate cancer (3+4 > 10%)

	Men With Negative/ Equivocal MRI (PRIMARY2) Australia RCT – 2 arms			prostate cancer who have undergone mpMRI in last 9 months and have **PIRADS 3 lesion or PIRADS 2 lesion and a red flag** eg PSAD > 0.1 or abnormal DRE	If positive targeted transperineal prostate biopsies. If negative no biopsy - PSA monitoring only.		Biopsies avoided with intervention *Secondary* Clinically insignificant prostate cancer Health economic impact Health-related quality of life Anxiety and cancer worry Number of biopsy cores Clinically significant prostate cancer – alternative definitions

CT= computed tomography; DRE = digital rectal examination; ISUP = International Society of Urological Pathology; mpMRI = multiparametric MRI; PET= positron emission tomography; PIRADS = prostate imaging reporting and data system; PSAD = PSA density; PSMA = prostate-specific membrane antigen

REFERENCES:

Buteau JP, Moon D, Fayeh MT et al. 2024 Clinical Trial Protocol for PRIMARY2: A Multicentre, Phase 3, Randomised Controlled Trial Investigating the Additive Diagnostic Value of [^{68}Ga]Ga-PSMA-11 Positron Emission Tomography/ Computed Tomography in Men with Negative or Equivocal Multiparametric Magnetic Resonance Imaging for the Diagnosis of Clinically Significant Prostate Cancer. Eur. Urol. Oncol. 7:544-552.

Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol. 2016 Feb;40(2):244-52.

Kohestani K, Mansson M, Godtman RA et al. 2021.The GOTEBORG prostate cancer screening 2 trial: a prospective, randomised population-based prostate cancer screening trial with prostate-specific antigen testing followed by magnetic resonance imaging of the prostate. Scand. J. Urol. 55:116-124.

Schunemann H, Brozek J, Guyatt G, Oxman A, eds. Handbook for grading the quality of evidence and the strength of recommendation using the GRADE approach. Updated October 2013.

Schunemann HJ, Neumann I, Hultcrantz M et al. 2022. GRADE guidance 35: Update on rating imprecision for assessing contextualized certainty of evidence and making decisions. J. Clin. Epidemiol. 150:225-242.

Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

APPENDICES

Appendix A: Literature search strategy

Databases: Medline, Embase and Cochrane Central Register of Controlled Trials databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or pathology* or histopathology* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	limit 15 to english language
17	limit 16 to yr="2010 -Current"
18	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
19	Randomized Controlled Trial/
20	exp Randomized Controlled Trials as Topic/
21	"Randomized Controlled Trial (topic)"/
22	Controlled Clinical Trial/
23	exp Controlled Clinical Trials as Topic/
24	"Controlled Clinical Trial (topic)"/
25	Randomization/
26	Random Allocation/
27	Double-Blind Method/
28	Double Blind Procedure/
29	Double-Blind Studies/
30	Single-Blind Method/
31	Single Blind Procedure/
32	Single-Blind Studies/
33	Placebos/
34	Placebo/
35	Control Groups/
36	Control Group/
37	(random* or sham or placebo*).ti,ab,hw,kf.
38	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
39	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.

40	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
41	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
42	allocated.ti,ab,hw.
43	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
44	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
45	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
46	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
47	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
48	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
49	or/18-48
50	17 and 49

Appendix B: Potentially relevant prostate cancer early detection and management guidelines reported based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Did not directly consider using mpMRI alone or mpMRI in combination with PSA density to triage men to biopsy

Appendix C: Excluded Studies

Article	*DOI*	*Reason for exclusion*
Arsov 2022	https://dx.doi.org/10.1002/ijc.33940	Ineligible study design
Baccaglini 2020	https://dx.doi.org/10.1097/MOU.0000000000000801	Systematic review with different inclusion criteria
Baco 2016	https://dx.doi.org/10.1016/j.eururo.2015.03.041	No outcome of interest
Baur 2017	https://dx.doi.org/10.1016/j.cct.2017.03.001	Ineligible study design
Bjornebo 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.7131	Ineligible study design
Drost 2019	https://dx.doi.org/10.1002/14651858.CD012663.pub2	Systematic review with different inclusion criteria
Elwenspoek 2019	https://dx.doi.org/10.1001/jamanetworkopen.2019.8427	No outcome of interest
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	Systematic review with different inclusion criteria
Gayet 2016	https://dx.doi.org/10.1111/bju.13247	Ineligible study design
Goldberg 2020	https://dx.doi.org/10.1097/JU.0000000000000595	No outcome of interest
Haider 2021	https://dx.doi.org/10.1016/j.clon.2021.07.016	No outcome of interest
Haider 2022	https://dx.doi.org/10.5489/cuaj.7425	No outcome of interest
Hu 2020	https://dx.doi.org/10.1007/s00261-019-02370-z	No outcome of interest
Hugosson 2022	https://dx.doi.org/10.1056/NEJMoa2209454	Ineligible comparator
Jiang 2016	https://dx.doi.org/10.3892/mco.2016.906	Systematic review with different inclusion criteria
Kasivisvanathan 2015	https://dx.doi.org/10.1016/j.urolonc.2014.12.003	Ineligible publication type
Kasivisvanathan 2018	https://dx.doi.org/10.1056/NEJMoa1801993	No outcome of interest
Kasivisvanathan 2019	https://dx.doi.org/10.1016/j.eururo.2019.04.043	No outcome of interest
Klotz 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7589	No outcome of interest
Klotz 2023	https://dx.doi.org/10.1016/j.euo.2023.09.013	No outcome of interest
Kruger-Stokke 2021	https://dx.doi.org/10.3389/fonc.2021.745657	Ineligible study design
Merrett 2018	https://doi.org/10.1016/j.urology.2018.04.024	Ineligible publication type
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.07.019	No data reported for comparator

Nordström 2021	https://dx.doi.org/10.1016/S1470-2045(21)00348-X	Ineligible intervention
Panebianco 2015	https://dx.doi.org/10.1016/j.urolonc.2014.09.013	No outcome of interest
Park 2011	https://dx.doi.org/10.2214/AJR.11.6829	No outcome of interest
Petov 2023	https://dx.doi.org/10.3390/cancers15041181	Ineligible intervention
Porpiglia 2017	https://dx.doi.org/10.1016/j.eururo.2016.08.041	No outcome of interest
Rannikko 2024	https://doi.org/10.1016/S2666-1683(24)00452-X	Ineligible comparator
Sarkar 2018	https://dx.doi.org/10.1007/978-3-319-95693-0	Systematic review with different inclusion criteria
Tesfai 2024	https://dx.doi.org/10.1002/bco2.321	Systematic review with different inclusion criteria
Tonttila 2016	https://dx.doi.org/10.1016/j.eururo.2015.05.024	No outcome of interest
Tu 2020	https://dx.doi.org/10.1159/000504028	No outcome of interest
Wagensveld 2022	https://dx.doi.org/10.1016/j.eururo.2022.03.003	Ineligible study design
Wang 2023	https://dx.doi.org/10.1007/s00345-022-04086-0	No outcome of interest
Woo 2019	https://dx.doi.org/10.1016/j.euo.2019.05.004	No outcome of interest
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Ineligible population

3.9 Clinical question 7 – mpMRI PICO 7C

Clinical question: *Can/should we use mpMRI to triage men with no history of prostate cancer and an elevated PSA for biopsy?*

Systematic review report for PICO 7C: Diagnostic accuracy of multiparametric MRI plus PSA density vs multiparametric MRI alone for the detection of clinically significant prostate cancer in biopsy naïve men.

Authors

Chelsea Carle, Isabel Rewais, Susan Yuill, Michael David, Suzanne Hughes

PICO 7C

This systematic review addresses the following PICOs which are summarised in detail in Tables 1a and 1b.

PICO 7Ca. *For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, how does triage using mpMRI with or without PSA density using a threshold of 0.15 µg/L/mL compare with triage using mpMRI alone and with all individuals undergoing biopsy for diagnostic accuracy outcomes?*

PICO 7Cb. *For individuals with no history of prostate cancer with elevated PSA levels and who are biopsy-naïve, how does triage using mpMRI with or without PSA density using a threshold of 0.15 or 0.20 µg/L/mL compare with triage using mpMRI alone and with all individuals undergoing biopsy for diagnostic accuracy outcomes?*

Table 20a. *PICO 7Ca components*

Study design	*Population*	*Index Test 1*	*Index Test 2*	*Reference standard*	*Outcomes#*
Cross-sectional diagnostic accuracy studies, or systematic reviews thereof	Individuals with no history of prostate cancer with elevated PSA levels undergoing initial prostate biopsy (biopsy naïve)	mpMRI PIRADS* ≥ 3 or PSA density ≥ 0.15 ng/ml^2 mpMRI PIRADS* ≥ 4 or PSA density ≥ 0.15 ng/ml^2	mpMRI PIRADS* ≥ 3 mpMRI PIRADS* ≥ 4	Systematic biopsy ≥ 20 cores +/- targeted biopsies	Diagnostic performance related to ISUP grade ≥ 2 prostate cancer ISUP grade 1 prostate cancer ISUP grade ≥ 3 prostate cancer

ISUP = International society of Urologic pathology; PIRADS = Prostate Image-Reporting and Data System
* Or Likert 1-5 scale
# Overall, or by age, PSA level or risk

Table 21b. *PICO 7Cb components*

Study design	*Population*	*Index Test 1*	*Index Test 2*	*Reference standard*	*Outcomes#*
Cross-sectional diagnostic accuracy studies, or systematic reviews thereof	Individuals with no history of prostate cancer with elevated PSA levels undergoing initial prostate biopsy (biopsy naïve)	mpMRI PIRADS* ≥ 3 or PSA density ≥ 0.15 or 0.20 ng/ml^2 mpMRI PIRADS* ≥ 4 or PSA density ≥ 0.15 or 0.20 ng/ml^2	mpMRI PIRADS* ≥ 3 mpMRI PIRADS* ≥ 4	Systematic biopsy ≥ 20 cores +/- targeted biopsies	Diagnostic performance related to ISUP grade ≥ 2 prostate cancer ISUP grade 1 prostate cancer ISUP grade ≥ 3 prostate cancer

ISUP = International society of Urologic pathology; PIRADS = Prostate Image-Reporting and Data System
* Or Likert 1-5 scale
# Overall, or by age, PSA level or risk

1. Methods

1.1 Selection Criteria

Table 22. *Selection criteria for systematic review of the diagnostic accuracy of multiparametric MRI combined with PSA density, compared to multiparametric MRI alone for the diagnosis of clinically significant prostate cancer in biopsy naïve men*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Diagnostic accuracy	
Study design	Cross-sectional head-to-head studies, or systematic reviews thereof	Diagnostic case-control studies or studies of diagnostic yield.
Population	Individuals with a clinical suspicion of prostate cancer due to elevated PSA levels or abnormal DRE undergoing initial prostate biopsy (biopsy naïve) including age, PSA level or risk level restricted subgroups	Clinical suspicion based on positive DRE only (not based on PSA test). Patients had prior biopsy (negative or positive) Individuals with prior prostate cancer diagnosis. > 10% of population have undergone prior biopsy and outcomes not for stratified for biopsy-naïve patients.
Index Test 1	Index test 2 or **PSA density ≥ 0.15 or 0.20** ng/ml^2	
Index Test 2	mpMRI (T2-weighted imaging + DWI + DCE) prior to biopsy and a score ≥3, or ≥4 on PIRADS v1, v2 or v2.1 or 5-point Likert scale	Biparametric mpMRI (no DCE). mpMRI includes MRS and results not available for mpMRI alone. Not 5-point Likert scale. mpMRI threshold unclear or not reported.
Reference Standard	≥ 20 core systematic (includes template and saturation biopsies) biopsy* regardless of index test results +/- mpMRI-targeted biopsy^ if targeted biopsies undertaken **Study must include and report results for both mpMRI positive and negative patients.** *transperineal or transrectal biopsy approach accepted ^any targeted biopsy approach accepted (fusion/software registration, cognitive, in-bore)	Systematic or template biopsy < 20 cores Systematic biopsy excludes regions sampled by targeted biopsy. Only mpMRI positive patients underwent biopsy, or only results for mpMRI positive patients reported i.e., no results reported for patients who were mpMRI negative. Radical prostatectomy specimen (restricted to patients with prostate cancer diagnosis).
Outcome	Sensitivity** and specificity^^ for prostate cancer: **ISUP grade ≥ 2 (primary outcome)**, or ISUP grade ≥ 3, or ISUP grade 1 Overall or by age, PSA level or risk subgroups **must report sufficient data to calculate TP and FN for sensitivity ^^must report sufficient data to calculate TN and FP for specificity	PPV, NPV ISUP grade ≥ 2 combined with a subgroup of ISUP grade 1 for example • Maximum CCL ≥ 5 mm for Gleason score 6 disease • Maximum CCL ≥ 5 mm.
Analyses	Per-patient	Per-lesion
Publication date	From 1st January 1990	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

CCL = cancer core length; DCE = dynamic contrast enhancement; DRE = digital rectal examination; DWI = diffusion weighted imaging; FP = false positive: FN = false negative; ISUP = International Society of Urologic Pathology; MRS = magnetic resonance spectroscopy; PIRADS = Prostate Image-Reporting and Data System; TN = true negative; TP = true positive

1.2 Definitions and terminology

For the purposes of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

False negative refers to individuals with the outcome of interest who were index test negative.
False positive refers to individuals who did not have the outcome of interest who were index test positive.
ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).
ISUP grade ≥ 3 prostate cancer is prostate cancer scored as Gleason Score 7(4+3) or higher on histopathological findings (Epstein 2016).
ISUP grade 1 prostate cancer is prostate cancer scored as Gleason Score 6(3+3) on histopathological findings (Epstein 2016).
Multi-parametric MRI (mpMRI) refers to an imaging protocol used to detect and characterise tissue abnormalities to determine the presence and severity of cancer. Prostate mpMRI acquisition includes T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging.
Prostate-specific antigen density (PSAD) refers to the level of serum total PSA divided by the prostate volume.
Systematic biopsy includes template and saturation biopsies.
Targeted biopsy refers to a multiparametric MRI-targeted biopsy using cognitive, software registration or in-bore image fusion techniques to identify target/s.

- Cognitive image fusion refers to the operator visually fusing MRI images and real time ultrasound pictures.
- Software registration image fusion refers to using software to fuse uploaded MRI images to real time ultrasound.
- In-bore image fusion refers to fusing prior MRI images and a real time MRI during biopsy.

True negative refers to individuals who did not have the outcome of interest who were index test negative.
True positive refers to individuals with the outcome of interest who were index test positive.

1.3 Guidelines searches

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature searches (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website

- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- *Urological Society of Australia and New Zealand (USANZ) website*
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, as the evidence for mpMRI triage continues to evolve, be based on literature published up until 2022 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

A search for systematic reviews of prostate mpMRI published from 2010 onwards in Medline, Embase and Cochrane Systematic Review databases (search strategies in Appendix A) yielded 255 records. Two relevant

systematic reviews were identified: Wang et al (2024) captured relevant literature published from 1st January 2012 to 31st December 2021; Drost et al (2019) captured relevant literature published from 1st January 1990 to 31st July 2018. We assessed studies included in the Wang 2024 and Drost 2019 systematic reviews for inclusion in our systematic review, and designed searches to identify diagnostic accuracy studies or systematic reviews thereof published from 2022 onwards. Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase databases, and Cochrane Database of Systematic Reviews were searched on 6th December 2023 combining text terms and database-specific subject headings for prostate cancer, multiparametric MRI and PSA density. Searches were limited to articles published in English from 1st January 2022 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st September 2024. All searches were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the search is included as Appendix A. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

Two reviewers independently extracted data from the included studies, with independent third-reviewer adjudication if needed. The following data was extracted from included studies: Country and year of publication; participant eligibility and age, PSA and PSA density levels, symptoms, family history of prostate cancer and indication for biopsy; details of mpMRI including sequences, magnetic strength, test positivity threshold and scoring system, and radiologist experience; details of PSA density threshold evaluated; details of biopsies undertaken including number of systematic and targeted cores; prevalence of clinically significant prostate cancer (ISUP grade ≥ 2 cancer); relevant outcomes reported and subgroup data available.
The following data were extracted and used to construct 2x2 tables: total participants with outcome, total without outcome, total index test positive, total index test negative, true positives, false positives, false negatives, and true negatives, for reported outcomes, by index test positivity thresholds of PIRADS/Likert ≥ 3 and ≥ 4, with or without additional thresholds of PSAD 0.15 or 0.20 ng/ml^2.

1.6 Risk of bias assessments

Two review authors independently evaluated the risk of bias in included studies using the Quality of Diagnostic Accuracy Studies-Comparative (QUADAS-C) tool (Yang 2021) (available at https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-c/). This tool is designed to assess the risk of bias in studies comparing the diagnostic accuracy of two different tests as well as a single test. It assesses the four sources of bias, patient selection, index test, reference standard, and flow and timing, included in the QUADAS-2 tool plus sources of bias arising from test comparisons.

1.7 Meta-analyses

The *metadta* command in Stata Version 18.0 (StataCorp 2023) was used to generate study-specific sensitivity and specificity and associated 95% confidence intervals, and summary estimates of sensitivity and specificity, using a fixed model with a 0.5 constant continuity correction for zero counts (Sankey 1996). The *metadta* command was also used to generate pooled summary estimates of relative sensitivity and specificity,

with their respective 95% confidence intervals for the two index tests. Forest plots were obtained to present the results graphically. Subgroup analyses were planned for age, PSA level and risk data, if available.

1.8 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for the sensitivity and specificity of multi-parametric MRI to detect the outcomes of interest.
(https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).
The certainty of the body of evidence for each critical outcomes was rated high, moderate, low or very low based on assessment of risk of selection bias, indirectness of the results, imprecision, inconsistency or heterogeneity of the results and publication bias following GRADE guidance provided by Schunemann 2020a, Schunemann 2020b and Schunemann 2022. Selection bias was considered an important source of bias for sensitivity and specificity estimates. Imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. These thresholds were determined by the clinical Working Group and following GRADE guidance provided by Schunemann 2022. Inconsistency was assessed based on the range of point estimates and a consideration of possible sources of heterogeneity. The I^2 statistic was not used to assess heterogeneity as it is designed to assess the heterogeneity of relative proportions not actual proportions and thus could be misleading for sensitivity and specificity estimates. Potential publication bias (or small study effects) was assessed for meta-analyses with 10 or more studies using the nonparametric “trim and fill” method (Duval 2000) implemented using the STATA command “metatrim”, following guidance provided by Schunemann 2020b; where there were less than 10 studies, potential conflicts of interest were considered.
As per GRADE guidance, studies started with a high level of certainty in the evidence and were downgraded in a stepwise manner from high to moderate to low to very low if there were serious concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.
Definitions of the GRADE ratings of certainty are presented in Appendix B.

2. Results

2.1 Guidelines searches

One potentially relevant guideline was identified which was based on systematic reviews of the literature published up until 2022 or later. It was not considered for adoption as it did not directly consider using mpMRI alone or combined with PSA density to triage men with elevated PSA levels to biopsy (Appendix C).

2.2 Literature searches

The systematic search for studies published from 2022 onwards identified 461 unique records to September 1st, 2024 (Figure 1). Of these, 73 full text articles were assessed independently by 2 reviewers. Eleven additional articles identified from reference lists of included articles, and 54 studies published to 2022 included in the Wang 2024 and Drost 2019 systematic reviews were also assessed for inclusion. Two studies reported in two articles met criteria for inclusion in our systematic review (Hansen 2018, Hogan 2022). There were no studies that reported including Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.

The retrieved articles that were not included in this update and the reasons for their exclusion are documented in Appendix D. The main reasons for exclusion were no reference standard of interest, or no population of interest.

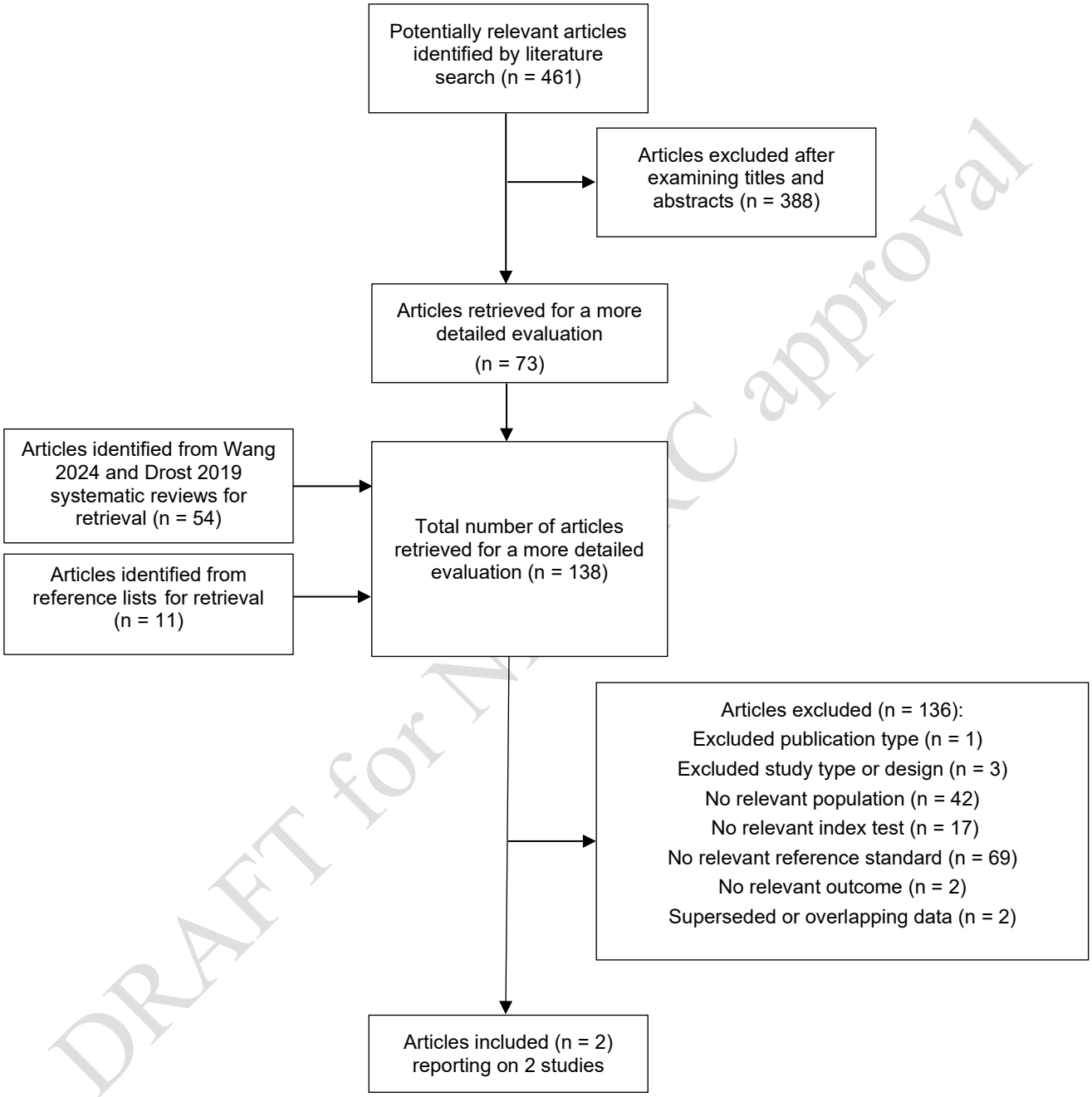

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

2.3 Characteristics of included studies

Table 23. *Study characteristics of included studies of diagnostic accuracy of multiparametric MRI and PSA density for the detection of clinically significant prostate cancer in biopsy naïve men.*

Study	*Participants*	*mpMRI*	*Positive mpMRI*	*PSA density*	*Systematic biopsy (SB)*	*Targeted biopsy (TB)*	*Reference standard*	*Prevalence CSPrCa*	*Outcomes of interest*
Hansen 2018 Germany, United Kingdom, Australia Prospective	Men aged <80 years who underwent mpMRI prior to biopsy at multiple tertiary centres in 2012-2016. Indication for biopsy: Elevated PSA (> age-related normal range) 43%, abnormal DRE 6%, elevated PSA and abnormal DRE 43%, other indications including family history 7% **N = 807** Initial biopsy: 100% Age median (IQR): 65 (59-70) years PSA median (IQR): 6.5 (4.9-8.8) ng/ml PSAD median (IQR): 0.15 (0.1-0.22) ng/ml/L Symptomatic: NR Family history prostate cancer: NR	T1WI + T2WI + DWI + DCE 1.5 or 3.0T field strength	≥3 on PIRADS v1 (pre-2015) or v2 (2015 onwards) N = 571 (71%) Determined by radiologists with team-based peer-review of images in equivocal cases and ongoing histological feedback on >150 MRI/year.	0.10, 0.15, 0.20 ng/ml/ml thresholds Calculation method NR	Transperineal Ginsburg protocol: 3-4 cores per each of 6 prostate sectors using 5mm brachytherapy grid	Transperineal TRUS-**Fusion** TB (2 centres) or **Cognitive** TB (1 centre) Prior to SB ≥2 cores per lesion Median (IQR) **4 (2-5) cores** per patient	**SB+TB** Median (IQR) **26 (24-28) cores**	48.6% (392/807)	**ISUP G ≥ 2** *Reported as Gleason Score* Pathologist blinding NR
Hogan 2022 Australia Retrospective	Men who underwent mpMRI prior to biopsy at a single tertiary centre in 2017-2018. Indication for biopsy: Elevated PSA (threshold and % NR) or abnormal DRE 33% **N = 140** Initial biopsy: 100% Age mean (SD): 61.3 (9.65) years PSA median (IQR): 6 (4.5-8.8) ng/ml PSAD median (IQR): 0.15 (0.09-0.26) ng/ml/L Symptomatic: LUTS 45.7% Family history prostate cancer: 14.3%	T1WI + T2WI + DWI + DCE 3.0T field strength with external phased array body coil (>90%)	≥3 on PIRADS v2 N = 97 (69%) Determined by a single radiologist with 7 years' experience reporting on prostate MRIs	0.15 ng/ml/ml threshold 0.10, 0.20 ng/ml/ml thresholds *not extractable** Calculation method NR	Transperineal using 5mm brachytherapy grid Number of cores: NR	Transperineal **Cognitive** TB NR if prior to SB Number of cores per patient: NR 42/97 (43%) mpMRI positive underwent TB. 55/97 had PIRADS 3-5 lesions sampled as part of SB.	**SB+TB** Median (IQR) **26 (22-33) cores** per patient	28.6% (40/140)	**ISUP G ≥ 2** ISUP ≥ 3 *not extractable** Pathologist blinding NR

3T = 3 tesla; CSPrCa = clinically significant prostate cancer; DCE = dynamic contrast enhancement; DRE = digital rectal examination; DWI = diffusion weighted imaging; IQR = interquartile range ISUP G = International Society of Urological Pathology grade; LUTS = lower urinary tract symptoms; NR = not reported; PIRADS = Prostate Image-Reporting and Data System; SB = systematic biopsy; SD = standard deviation; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging; TB = MRI-targeted biopsy; TRUS = transrectal ultrasound
*Request to authors for additional data not successful

2.4 Results by outcome of interest

Results for diagnostic performance (sensitivity and specificity) related to the detection of

ISUP grade ≥ 2 prostate cancer – Table 4, Figures 2-5

ISUP grade ≥ 3 prostate cancer – No results

ISUP grade 1 prostate cancer – No results

*Results for the detection of **clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer)***

Table 24. *Sensitivity and specificity of using both mpMRI and PSA density as indications for biopsy relative to the sensitivity and specificity of using mpMRI alone as an indication for biopsy for the detection of ISUP grade ≥ 2 prostate cancer) in biopsy naïve men*

Analysis	***Figure***	***Studies (N)***	***Participants (N)***	***ISUP ≥ 2 per 1000***	***Indications for biopsy (Definition of test positive)***	***Sensitivity*** *(95%CI)*	***Relative sensitivity*** *(95%CI)*	***Specificity*** *(95%CI)*	***Relative specificity*** *(95%CI)*
PSAD threshold 0.15 *ng/ml²*									
Meta-analysis	2	2	947	456	PI-RADS ≥ 3	0.88 (0.85, 0.91)	ref	0.44 (0.40, 0.49)	ref
					PI-RADS ≥ 3 or PI-RADS 1-2 and PSAD > 0.15 ng/ml²*	0.95 (0.92, 0.96)	1.07 (1.03, 1.12)	0.28 (0.25, 0.32)	0.64 (0.54, 0.76)
Meta-analysis	3	2	947	456	PI-RADS ≥ 4	0.77 (0.72, 0.80)	ref	0.71 (0.67, 0.74)	ref
					PI-RADS ≥ 4 or PI-RADS 1-3 and PSAD > 0.15 ng/ml²*	0.88 (0.85, 0.91)	1.15 (1.08, 1.23)	0.47 (0.42, 0.51)	0.66 (0.59, 0.73)
					PI-RADS ≥ 4 or PI-RADS 3 and PSAD > 0.15 ng/ml²*	0.82 (0.78, 0.86)	1.07 (1.00, 1.15)	0.63 (0.58, 0.67)	0.88 (0.81, 0.97)
PSAD threshold 0.20 *ng/ml²*									
Single study	4	1 (Hansen 2018)	807	486	PI-RADS ≥ 3	0.88 (0.84, 0.91)	ref	0.45 (0.40, 0.50)	ref
					PI-RADS ≥ 3 or PI-RADS 1-2 and PSAD > 0.20 ng/ml²	0.92 (0.89, 0.94)	1.05 (1.00, 1.10)	0.38 (0.33, 0.43)	0.84 (0.71, 0.98)
Single study	5	1 (Hansen 2018)	807	486	PI-RADS ≥4	0.76 (0.71, 0.80)	ref	0.71 (0.66, 0.75)	ref
					PI-RADS ≥ 4 or	0.83 (0.79, 0.87)	1.09 (1.02, 1.18)	0.60 (0.55, 0.65)	0.85 (0.77, 0.94)

					PI-RADS 1-3 and PSAD > 0.20 ng/ml^2				
					PI-RADS ≥ 4 or PI-RADS 3 and PSAD > 0.20 ng/ml^2	0.79 (0.74, 0.83)	1.04 (0.96, 1.12)	0.68 (0.63, 0.72)	0.96 (0.87, 1.05)

CI = confidence interval; mpMRI = multi-parametric magnetic resonance imaging; N = number; PIRADS = Prostate Image-Reporting and Data System; PSAD = PSA density; Ref = reference

* PSAD > 0.15 in one study and ≥ 0.15 in the other study

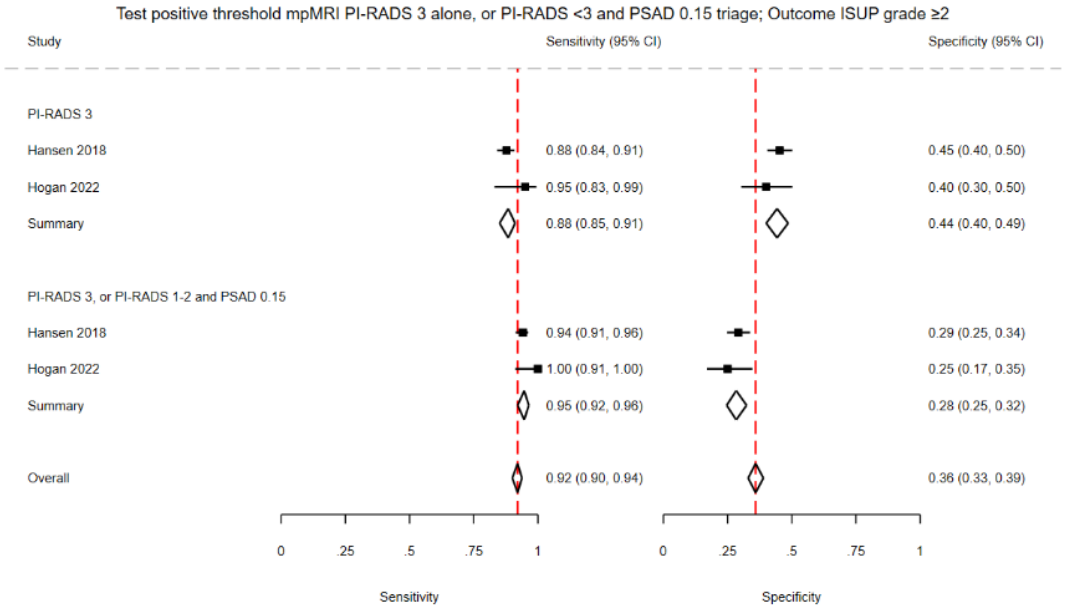

Figure 2. *Test positive threshold mpMRI PI-RADS 3 alone, or PI-RADS <3 and PSAD 0.15 ng/ml²* triage; Outcome ISUP grade ≥ 2*
* PSAD > 0.15 in one study and ≥ 0.15 in the other study
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

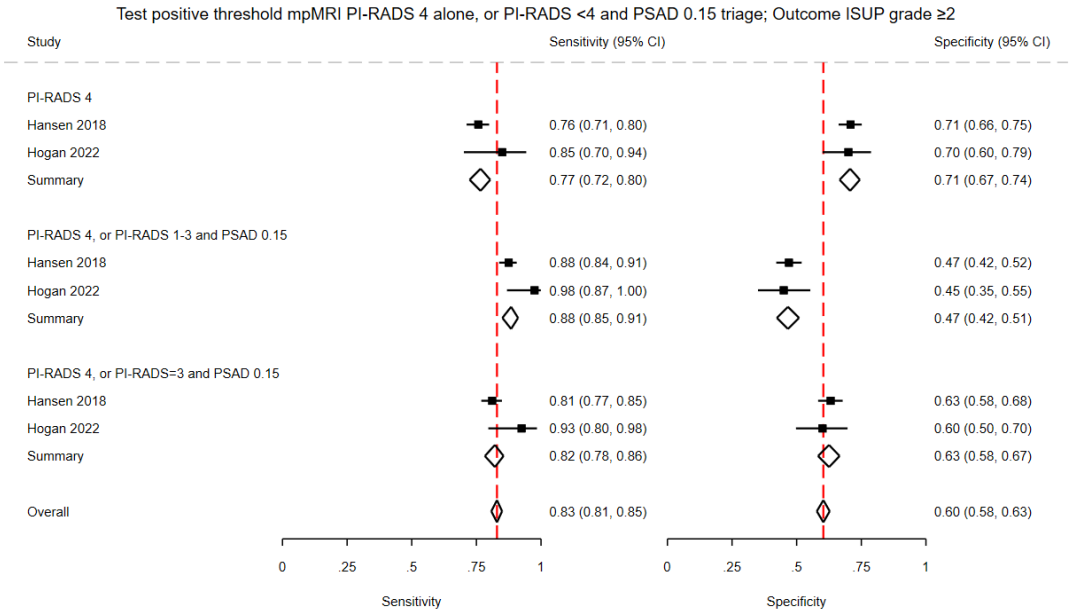

Figure 3. *Test positive threshold mpMRI PI-RADS 4 alone, or PI-RADS < 4 and PSAD 0.15 ng/ml²* triage; Outcome ISUP grade ≥2*
* PSAD > 0.15 in one study and ≥ 0.15 in the other study
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

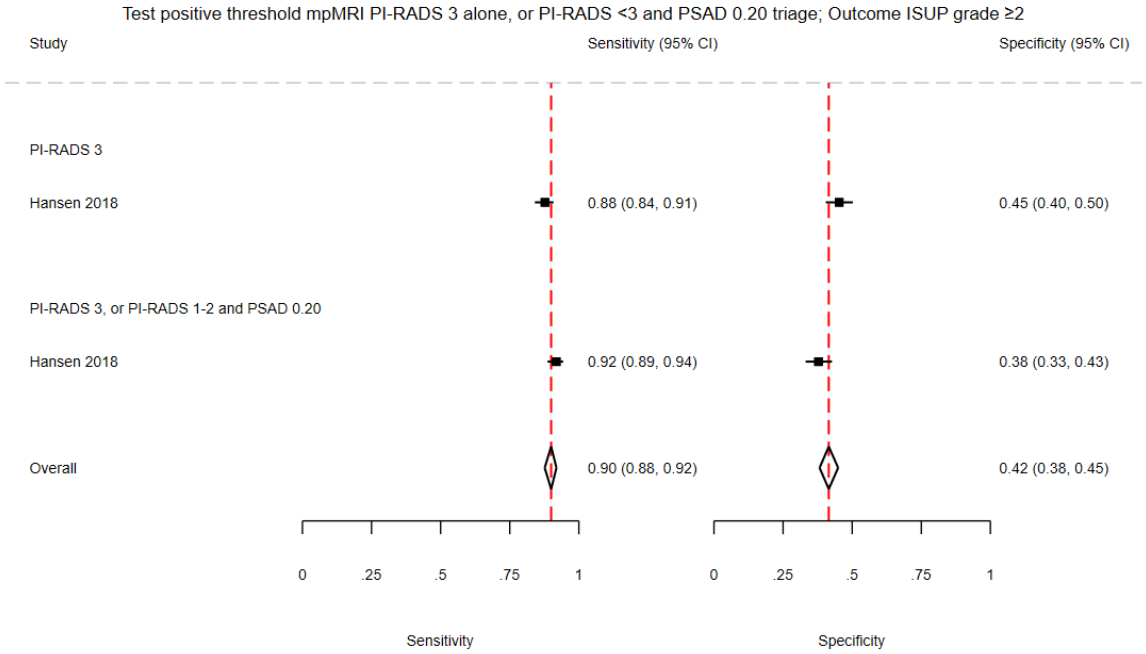

Figure 4. *Test positive threshold mpMRI PI-RADS 3 alone, or PI-RADS <3 and PSAD 0.20 ng/ml² triage; Outcome ISUP grade ≥ 2*
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

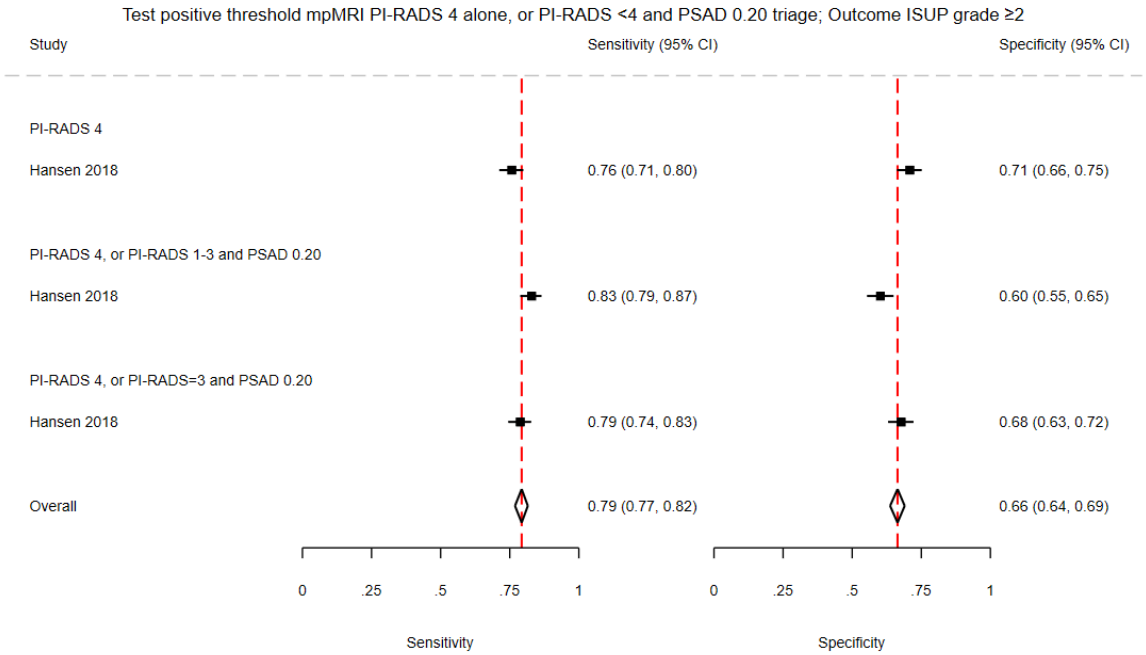

Figure 5. *Test positive threshold mpMRI PI-RADS 4 alone, or PI-RADS <4 and PSAD 0.20 ng/ml² triage; Outcome ISUP grade ≥ 2*
Note: Point estimate markers of each study are not weighted proportionally to the pooled estimate.

2.5 Risk of bias

The results of the risk of bias assessments for the included studies are shown in Table 5.

Table 5. *Risk of bias assessments for included diagnostic accuracy studies using the Quality of Diagnostic Accuracy Studies – Comparative (QUADAS-C) (Yang 2021) risk of bias assessment tool.*

Study	Test	Risk of bias (for each index test)				Risk of bias (for comparison of index tests)				Overall
		Patient selection	Index test	Reference standard	Flow and Timing	Patient selection	Index test	Reference standard	Flow and Timing	
Hansen 2018	mpMRI + PSAD	High	Low	Moderate	High	High	Low	High	High	High
	mpMRI	High	Low	Moderate	High					
Hogan 2022	mpMRI + PSAD	High	Low	Moderate	High	High	Low	High	High	High
	mpMRI	High	Low	Moderate	High					

mpMRI = multiparametric MRI; PSAD = PSA density

3. GRADE Certainty of the evidence

ISUP Grade ≥ 2 prostate cancer relative sensitivity and relative specificity - assessments are shown in Table 6
ISUP Grade ≥ 2 prostate cancer sensitivity and specificity - assessments are shown in Table 7

Table 6. *GRADE assessment of the certainty of the evidence for the increase in sensitivity (**relative sensitivity**) and decrease in specificity (**relative specificity**) with the addition of PSA density (> 0.15 or 0.20 ng/ml²) to multiparametric MRI to detect ISUP Grade ≥ 2 prostate cancer*

	Rating	***Reason for rating***	***Certainty of evidence***
Test positive threshold comparison: *PIRADS ≥ 3* ***or PIRADS 1-2 and PSAD > 0.15**** *ng/ml² vs PIRADS ≥ 3* (Table 4)			
Risk of bias	No serious concerns	Both studies at high risk of selection bias however this was not considered an important source of bias for relative sensitivity and relative specificity.	***Relative sensitivity*** **High** ***Relative specificity*** **Moderate**
Indirectness	No serious concerns	One of the two studies reported > 40% of population symptomatic. The remaining study did not report whether patients asymptomatic or symptomatic and the prevalence of clinically significant disease in this study was greater than that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* No serious concerns *Specificity* Serious concerns (-1)	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals, offering biopsy to men with a PIRADS of 1-2 and PSAD > 0.15 ng/ml² as well as to men with a PIRADS ≥ 3 is estimated to detect an additional 12 (5-21) ISUP Grade ≥ 2 prostate cancers and result in an additional 127 (84-163) unnecessary biopsies. For additional ISUP Grade ≥ 2 prostate cancer detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/100 the 95%CI did not cross any thresholds. For additional unnecessary biopsies using a MCID of 100/1000 and thresholds for moderate and large effects of 200/1000 and 400/1000, the 95%CI crossed one threshold.	
Inconsistency	No serious concerns	For PSAD > 0.15 ng/ml² range of point estimates ≤ 10 percentage points for increase in sensitivity and decrease in specificity.	
Publication bias	Not detected	Both studies either reported no direct funding by industry and/or declared no conflicts of interest.	
Test positive threshold comparison: *PIRADS ≥ 3* ***or PIRADS 1-2 and PSAD > 0.20*** *ng/ml² vs PIRADS ≥ 3* (Table 4)			
Risk of bias	No serious concerns	Single study at high risk of selection bias however this was not considered an important source of bias for relative sensitivity and relative specificity.	***Relative sensitivity*** **High** ***Relative specificity*** **Moderate**
Indirectness	No serious concerns	The study did not report whether patients asymptomatic or symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* No serious concerns *Specificity* Serious concerns (-1)	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals, offering biopsy to men with a PIRADS of 1-2 and PSAD > 0.20 ng/ml² as well as to men with a PIRADS ≥ 3 is estimated to detect an additional 9 (0-18) ISUP Grade ≥ 2 prostate cancers and result in an additional 58 (7-105) unnecessary biopsies. For additional ISUP Grade ≥ 2 prostate cancer detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/100 the 95%CI did not cross any thresholds. For additional unnecessary biopsies using a MCID of 100/1000 and thresholds for moderate and large effects of 200/1000 and 400/1000, the 95%CI crossed one threshold.	
Inconsistency	Not assessable	Not assessable as only one study.	

Publication bias	Not detected	Authors declared no conflicts of interest.	
Test positive threshold comparison: *PIRADS* ≥ *4* ***or PIRADS 1-3 and PSAD > 0.15**** *ng/ml^2 vs PIRADS* ≥ *4* (Table 4)			
Risk of bias	No serious concerns	Both studies at high risk of selection bias however this was not considered an important source of bias for relative sensitivity and relative specificity.	
Indirectness	No serious concerns	One of the two studies reported > 40% of population symptomatic. The remaining study did not report whether patients asymptomatic or symptomatic and the prevalence of clinically significant disease in this study was greater than that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* No serious concerns *Specificity* Serious concerns (-1)	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals, offering biopsy to men with a PIRADS of 1-3 and PSAD > 0.15 ng/ml^2 as well as to men with a PIRADS ≥ 4 is estimated to detect an additional 23 (12-35) ISUP Grade ≥ 2 prostate cancers and result in an additional 192 (153-232) unnecessary biopsies. For additional ISUP Grade ≥ 2 prostate cancer detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI did not cross any thresholds. For additional unnecessary biopsies using a MCID of 100/1000 and thresholds for moderate and large effects of 200 and 400, the 95%CI crossed one threshold.	***Relative sensitivity*** **High** ***Relative specificity*** **Moderate**
Inconsistency	No serious concerns	For PSAD > 0.15 ng/ml^2 range of point estimates ≤ 10 percentage points for increase in sensitivity and decrease in specificity.	
Publication bias	Not detected	Both studies either reported no direct funding by industry and/or declared no conflicts of interest.	
Test positive threshold comparison: *PIRADS* ≥ *4* ***or PIRADS 1-3 and PSAD > 0.20*** *ng/ml^2 vs PIRADS* ≥ *4* (Table 4)			
Risk of bias	No serious concerns	Single study at high risk of selection bias however this was not considered an important source of bias for relative sensitivity and relative specificity.	
Indirectness	No serious concerns	The study did not report whether patients asymptomatic or symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* No serious concerns *Specificity* Serious concerns (-1)	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals, offering biopsy to men with a PIRADS of 1-3 and PSAD > 0.20 ng/ml^2 as well as to men with a PIRADS ≥ 4 is estimated to detect an additional 14 (3-27) ISUP Grade ≥ 2 prostate cancers and result in an additional 85 (34-130) unnecessary biopsies. For additional ISUP Grade ≥ 2 prostate cancer detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/100 the 95%CI did not cross any thresholds. For additional unnecessary biopsies using a MCID of 100/1000 and thresholds for moderate and large effects of 200/1000 and 400/1000, the 95%CI crossed one threshold.	***Relative sensitivity*** **High** ***Relative specificity*** **Moderate**
Inconsistency	Not assessable	Not assessable as only one study.	
Publication bias	Not detected	Authors declared no conflicts of interest.	
Test positive threshold comparison: *PIRADS* ≥ *4* ***or PIRADS 3 and PSAD > 0.15**** *ng/ml^2 vs PIRADS* ≥ *4* (Table 4)			
Risk of bias	No serious concerns	Both studies at high risk of selection bias however this was not considered an important source of bias for relative sensitivity and relative specificity	***Relative sensitivity*** **High**
Indirectness	No serious concerns	One of the two studies reported > 40% of population symptomatic. The remaining study did not report whether patients asymptomatic or symptomatic and the prevalence of clinically significant disease in this study was greater than that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	***Relative specificity*** **Moderate**

Imprecision	*Sensitivity* No serious concerns *Specificity* Serious concerns (-1)	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals, offering biopsy to men with a PIRADS of 3 and PSAD > 0.15 ng/ml^2 as well as to men with a PIRADS ≥ 4 is estimated to detect an additional 11 (0-23) ISUP Grade ≥ 2 prostate cancers and result in an additional 68 (17-108) unnecessary biopsies. For additional ISUP Grade ≥ 2 prostate cancer detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI did not cross any thresholds. For additional unnecessary biopsies using a MCID of 100/1000 and thresholds for moderate and large effects of 200 and 400, the 95%CI crossed one threshold.	
Inconsistency	No serious concerns	For PSAD > 0.15 ng/ml^2 range of point estimates ≤ 10 percentage points for increase in sensitivity and decrease in specificity.	
Publication bias	Not detected	Both studies either reported no direct funding by industry and/or declared no conflicts of interest.	
Test positive threshold comparison: *PIRADS ≥ 4* ***or PIRADS 3 and PSAD > 0.20*** *ng/ml^2 vs PIRADS ≥ 4* (Table 4)			
Risk of bias	No serious concerns	Single study at high risk of selection bias however this was not considered an important source of bias for relative sensitivity and relative specificity.	
Indirectness	No serious concerns	The study did not report whether patients asymptomatic or symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* Serious concerns (-1) *Specificity* Serious concerns (-1)	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals, offering biopsy to men with a PIRADS of 3 and PSAD > 0.20 ng/ml^2 as well as to men with a PIRADS ≥ 4 is estimated to detect 6 additional (6 less-18 additional) ISUP Grade ≥ 2 prostate cancers and result in 23 additional (28 less-74 additional) unnecessary biopsies. For additional ISUP Grade ≥ 2 prostate cancer detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/100 the 95%CI crossed the threshold for no effect. For additional unnecessary biopsies using a MCID of 100/1000 and thresholds for moderate and large effects of 200/1000 and 400/1000, the 95%CI crossed the threshold for no effect.	
Inconsistency	Not assessable	Not assessable as only one study.	
Publication bias	Not detected	Authors declared no conflicts of interest.	

CI = confidence interval; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; mpMRI = multiparametric MRI; PIRADS = prostate image-reporting and data system; PSAD = PSA density
** PSAD > 0.15 in one study and ≥ 0.15 in the other study*

Table 7. *GRADE assessment of the certainty of the evidence for the* ***sensitivity*** *and* ***specificity*** *of different triage protocols to detect ISUP Grade ≥ 2 prostate cancer*

	Rating	***Reason for rating***	***Certainty of evidence***
Biopsy if ***PIRADS ≥ 3 or PIRADS 1-2 and PSAD > 0.15**** *ng/ml^2 (Figure 2)*			
Risk of bias	Serious concerns (-1)	Both studies at high risk of selection bias.	***Sensitivity*** **Moderate** ***Specificity*** **Moderate**
Indirectness	No serious concerns	One of the two studies reported > 40% of population symptomatic. The remaining study did not report whether patients asymptomatic or symptomatic and the prevalence of clinically significant disease in this study was greater than that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	

Imprecision	*Sensitivity* No serious concerns *Specificity* No serious concerns	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals undergoing triage using a mpMRI-positivity threshold of PIRADS ≥ 3 or PIRADS 1-2 and PSAD > 0.15 ng/ml^2, 11 (8-16) ISUP Grade ≥ 2 prostate cancers not detected and 226 (200-256) unnecessary biopsies avoided. For ISUP Grade ≥ 2 prostate cancer undetected, using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI did not cross any thresholds. For unnecessary biopsies avoided, using a MCID of 100/1000 and thresholds for moderate and large effects of 200 and 400, the 95%CI did not cross any thresholds.	
Inconsistency	No serious concerns	Range of point estimates ≤ 10 percentage points for sensitivity and specificity	
Publication bias	Not detected	Both studies either reported no direct funding by industry and/or declared no conflicts of interest.	
*Biopsy if **PIRADS ≥ 4 or PIRADS 1-3 and PSAD > 0.15* ng/ml^2** (Figure 3)*			
Risk of bias	Serious concerns (-1)	Both studies at high risk of selection bias.	
Indirectness	No serious concerns	One of the two studies reported > 40% of population symptomatic. The remaining study did not report whether patients asymptomatic or symptomatic and the prevalence of clinically significant disease in this study was greater than that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* No serious concerns *Specificity* Serious concerns (-1)	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals undergoing triage using a mpMRI-positivity threshold of PIRADS ≥ 4 or PIRADS 1-3 and PSAD > 0.15 ng/ml^2, 23 (18-30) ISUP Grade ≥ 2 prostate cancers not detected and 373 (336-408) unnecessary biopsies avoided. For ISUP Grade ≥ 2 prostate cancer undetected, using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI did not cross any thresholds^. For unnecessary biopsies avoided, using a MCID of 100/1000 and thresholds for moderate and large effects of 200 and 400, the 95%CI crossed one threshold^.	***Sensitivity*** **Moderate** ***Specificity*** **Low**
Inconsistency	No serious concerns	Range of point estimates ≤ 10 percentage points for sensitivity and specificity	
Publication bias	Not detected	Both studies either reported no direct funding by industry and/or declared no conflicts of interest.	
*Biopsy if **PIRADS ≥ 4 or PIRADS 1-3 and PSAD > 0.20 ng/ml^2** (Figure 5)*			
Risk of bias	Serious concerns (-1)	Study at high risk of selection bias	
Indirectness	No serious concerns	The study did not report whether patients asymptomatic or symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* No serious concerns *Specificity* No serious concerns	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals undergoing triage using a mpMRI-positivity threshold of PIRADS ≥ 4 or PIRADS 1-3 and PSAD > 0.20 ng/ml^2, 34 (26-42) ISUP Grade ≥ 2 prostate cancers not detected and 482 (440-520) unnecessary biopsies avoided. For ISUP Grade ≥ 2 prostate cancer undetected, using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI did not cross any thresholds. For unnecessary biopsies avoided, using a MCID of 100/1000 and thresholds for moderate and large effects of 200 and 400, the 95%CI did not cross any thresholds.	***Sensitivity*** **Moderate** ***Specificity*** **Moderate**
Inconsistency	Not assessable	Not assessable as only one study.	
Publication bias	Not detected	Authors declared no conflicts of interest.	
*Biopsy if **PIRADS ≥ 3** (Figure 2)*			
Risk of bias	Serious concerns (-1)	Both studies at high risk of selection bias.	***Sensitivity***

Indirectness	No serious concerns	One of the two studies reported > 40% of population symptomatic. The remaining study did not report whether patients asymptomatic or symptomatic and the prevalence of clinically significant disease in this study was greater than that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	**Moderate** ***Specificity*** **Moderate**
Imprecision	*Sensitivity* No serious concerns *Specificity* No serious concerns	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals undergoing triage using a mpMRI-positivity threshold of PIRADS ≥ 3, 23 (18-30) ISUP Grade ≥ 2 prostate cancers not detected and 354 (320-392) unnecessary biopsies avoided. For ISUP Grade ≥ 2 prostate cancer undetected, using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI did not cross any thresholds. For unnecessary biopsies avoided, using a MCID of 100/1000 and thresholds for moderate and large effects of 200 and 400, the 95%CI did not cross any thresholds.	
Inconsistency	No serious concerns	Range of point estimates ≤ 10 percentage points for sensitivity and specificity	
Publication bias	Not detected	Both studies either reported no direct funding by industry and/or declared no conflicts of interest.	
*Biopsy if **PIRADS ≥ 4 or PIRADS 3 and PSAD > 0.15 ng/ml^2** (Figure 3)*			
Risk of bias	Serious concerns (-1)	Both studies at high risk of selection bias.	
Indirectness	No serious concerns	One of the two studies reported > 40% of population symptomatic. The remaining study did not report whether patients asymptomatic or symptomatic and the prevalence of clinically significant disease in this study was greater than that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* No serious concerns *Specificity* No serious concerns	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals undergoing triage using a mpMRI-positivity threshold of PIRADS ≥ 4 or PIRADS 3 and PSAD > 0.15 ng/ml^2, 36 (28-44) ISUP Grade ≥ 2 prostate cancers not detected and 500 (464-536) unnecessary biopsies avoided. For ISUP Grade ≥ 2 prostate cancer undetected, using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI did not cross any thresholds^. For unnecessary biopsies avoided, using a MCID of 100/1000 and thresholds for moderate and large effects of 200 and 400, the 95%CI did not cross any thresholds^.	***Sensitivity*** **Moderate** ***Specificity*** **Moderate**
Inconsistency	No serious concerns	Range of point estimates ≤ 10 percentage points for specificity but not sensitivity^^. The differences in point estimates for sensitivity were not considered a serious concern as, based on sensitivity estimates derived from each of the two studies, in a population of 1000 people with a 20% prevalence of ISUP Grade ≥ 2 prostate cancer undergoing triage using this protocol, in both studies the number of ISUP Grade ≥ 2 cancers undetected (14 and 38) would be clinically unimportant.	
Publication bias	Not detected	Both studies either reported no direct funding by industry and/or declared no conflicts of interest.	
*Biopsy if **PIRADS ≥ 4 or PIRADS 3 and PSAD > 0.20 ng/ml^2** (Figure 5)^^*			
Risk of bias	Serious concerns (-1)	Study at high risk of selection bias	
Indirectness	No serious concerns	The study did not report whether patients asymptomatic or symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* Serious concerns (-1) *Specificity* No serious concerns	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals undergoing triage using a mpMRI-positivity threshold of PIRADS ≥ 4 or PIRADS 3 and PSAD > 0.20 ng/ml^2, 42 (34-52) ISUP Grade ≥ 2 prostate cancers not detected and 542 (504-576) unnecessary biopsies avoided. For ISUP Grade ≥ 2 prostate cancer undetected, using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI crossed one threshold.	***Sensitivity*** **Low** ***Specificity*** **Moderate**

		For unnecessary biopsies avoided, using a MCID of 100/1000 and thresholds for moderate and large effects of 200 and 400, the 95%CI did not cross any thresholds.	
Inconsistency	Not assessable	Not assessable as only one study.	
Publication bias	Not detected	Authors declared no conflicts of interest.	
*Biopsy if **PIRADS ≥ 4** (Figure 3)*			
Risk of bias	Serious concerns (-1)	Both studies at high risk of selection bias.	
Indirectness	No serious concerns	One of the two studies reported > 40% of population symptomatic. The remaining study did not report whether patients asymptomatic or symptomatic and the prevalence of clinically significant disease in this study was greater than that in the study reporting > 40% of population symptomatic. This was not considered an issue when assessing diagnostic accuracy of mpMRI.	
Imprecision	*Sensitivity* Serious concerns (-1) *Specificity* No serious concerns	If prevalence of ISUP Grade ≥ 2 prostate cancer is 20%, in a population of 1000 individuals undergoing triage using a mpMRI-positivity threshold of PIRADS ≥ 4, 47 (40-56) ISUP Grade ≥ 2 prostate cancers not detected and 566 (536-592) unnecessary biopsies avoided. For ISUP Grade ≥ 2 prostate cancer undetected, using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI crossed one threshold^. For unnecessary biopsies avoided, using a MCID of 100/1000 and thresholds for moderate and large effects of 200 and 400, the 95%CI did not cross any thresholds^.	***Sensitivity*** **Low** ***Specificity*** **Moderate**
Inconsistency	No serious concerns	Range of point estimates ≤ 10 percentage points for sensitivity and specificity^^	
Publication bias	Not detected	Both studies either reported no direct funding by industry and/or declared no conflicts of interest.	

CI = confidence interval; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; mpMRI = multiparametric MRI; PI-RADS = prostate image-reporting and data system; PSAD = PSA density
** PSAD > 0.15 in one study and ≥ 0.15 in the other study*
^ same for single study Hansen 2018
^^ not an issue for single study Hansen 2018

4. Summary of findings

Table 8. *Summary of findings for **different protocols for triaging men to biopsy** using mpMRI with or without PSAD when **compared with no triage to biopsy** (i.e. all men undergo biopsy regardless of MRI result) **in the same cohorts,** if the prevalence amongst men with elevated PSA levels of ISUP Grade ≥ 2 prostate cancer is 10%, 20% or 30%. Protocols are ordered by increasing number of clinically significant cancers undetected.*

Outcome	***Studies (Participants)***	***Certainty of the evidence (GRADE)***	***Triage protocol:*** *mpMRI +/- PSAD positive threshold for biopsy* *(Flowcharts in Figures 6-10 after table)*	***Summary sensitivity*** *(95% CI)*	***Summary specificity*** *(95% CI)*	***Implications in a population of 1000 individuals with elevated PSA levels with disease prevalence^ of:***									***Plain text summary^^***
						10%			***20%***			***30%***			
						csPrCas undetected (95% CI)	*Unnecessary biopsies avoided (95% CI)*	*NPV*	*csPrCas undetected (95% CI)*	*Unnecessary biopsies avoided (95% CI)*	*NPV*	*csPrCas undetected (95% CI)*	*Unnecessary biopsies avoided (95% CI)*	*NPV*	Using mpMRI with or without PSAD to triage men to biopsy increases the number of clinically significant cancers undetected and the number of unnecessary biopsies avoided when compared to no triage
ISUP Grade ≥ 2	2 (947)	Moderate[a]	***Protocol 1*** No biopsy if PIRADS 1-2 and PSAD < 0.15 ng/ml[2] *(Figure 6)*	0.947 (0.92, 0.96)	0.283 (0.25, 0.32)	5 (4, 8)	255 (225, 288)	0.981	11 (8, 16)	226 (200, 256)	0.954	16 (12, 24)	198 (175, 224)	0.925	If do not biopsy men with a PIRADS of 1-2 who have a PSAD < 0.15 the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant ** and the number of unnecessary biopsies avoided is likely moderate#
ISUP Grade ≥ 2	2 (947)	*Sensitivity* Moderate[a] *Specificity* Low[b]	***Protocol 2*** No biopsy if PIRADS 1-3 and PSAD < 0.15 ng/ml[2] *(Figure 7)*	0.884 (0.85, 0.91)	0.466 (0.42, 0.51)	12 (9, 15)	419 (378, 459)	0.972	23 (18, 30)	373 (336, 408)	0.942	35 (27, 45)	326 (294, 357)	0.903	If do not biopsy men with a PIRADS 1-3 who have a PSAD < 0.15 the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant** and the number of unnecessary biopsies avoided may be moderate#.
ISUP Grade ≥ 2	2 (947)	Moderate[a]	***Protocol 3*** No biopsy if PIRADS 1-2 *(Figure 8)*	0.884 (0.85, 0.91)	0.443 (0.40, 0.49)	12 (9, 15)	399 (360, 441)	0.971	23 (18, 30)	354 (320, 392)	0.939	35 (27, 45)	310 (280, 343)	0.899	If do not biopsy men with a PIRADS of 1-2 the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant** and the number of unnecessary biopsies avoided is likely moderate#
ISUP Grade ≥ 2	2 (947)	Moderate[a]	***Protocol 4*** No biopsy if PIRADS 1-2 or PIRADS 3 and PSAD < 0.15 ng/ml[2] *(Figure 9)*	0.822 (0.78, 0.86)	0.625 (0.58, 0.67)	18 (14, 22)	563 (522, 603)	0.969	36 (28, 44)	500 (464, 536)	0.933	53 (42, 66)	438 (406, 469)	0.892	If do not biopsy men with a PIRADS of 1-2, or men with a PIRADS of 3 and a PSAD < 0.15, the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant** and the number of unnecessary biopsies avoided is likely large#
ISUP Grade ≥ 2	2 (947)	*Sensitivity* Low[b]	***Protocol 5*** No biopsy if	0.766 (0.72, 0.80)	0.707 (0.67, 0.74)	23 (20, 28)	636 (603, 666)	0.965	47 (40, 56)	566 (536, 592)	0.923	70 (60, 84)	495 (469, 518)	0.876	If do not biopsy men biopsy with a PIRADS of 1-3 the number of

		Specificity Moderate[a]	PIRADS 1-3 *(Figure 10)*												undetected ISUP Grade ≥ 2 prostate cancer may be clinically unimportant** and the number of unnecessary biopsies avoided is likely large#

CI = confidence interval; csPrCa = clinically significant prostate cancer; ISUP = International Society of Urological Pathology; NPV = negative predictive value; PIRADS = prostate image-reporting and data system
Clinically significant cancers undetected are the number ISUP grade ≥ 2 prostate cancers not detected by the index test (false negatives); this is a non-desirable outcome of mpMRI triage.
Unnecessary biopsies avoided are the number of index test negative (mpMRI ± PSAD results below the specified threshold for biopsy) individuals without ISUP grade ≥ 2 prostate cancers detected (true negatives) for whom it would be acceptable to avoid biopsy; this is a desirable outcome of mpMRI triage.
NPV is the proportion of individuals without ISUP grade ≥ 2 prostate cancers detected (true negatives) among the total number of index test negative individuals. Note this metric is dependent on the underlying outcome prevalence.
^ Implications are calculated for a range of prevalences as there are no data on the prevalence of this outcome in populations of individuals with elevated PSA levels in Australia.
^^ If prevalence of ISUP Grade ≥ 2 prostate cancer for men with elevated PSA levels is 20%
*** Using thresholds of 50, 100 and 200 undetected ISUP Grade ≥ 2 prostate cancer/1000 for small (minimal clinically important difference; MCID), moderate and large effects*
 # Using thresholds of 100, 200 and 400 unnecessary biopsies/1000 for small (MCID), moderate and large effects
[a] Serious concerns re selection bias
[b] Serious concerns re selection bias and imprecision

Table 9. *Summary of findings for **different protocols for triaging men to biopsy** using mpMRI with or without PSAD including additional protocols using a PSA density threshold of 0.2 ng/ml² when compared with no triage to biopsy (i.e. all men undergo biopsy regardless of MRI result) **in a single cohort,** if the prevalence amongst men with elevated PSA levels of ISUP Grade ≥ 2 prostate cancer is 20%. Protocols are ordered by increasing number of clinically significant cancers undetected.*

Outcome	***Studies (Participants)***	***Certainty of the evidence (GRADE)***	***Triage protocol:*** *mpMRI +/- PSAD positive threshold for biopsy*	***Sensitivity*** *(95% CI)*	***Specificity*** *(95% CI)*	***Implications in a population of 1000 individuals with elevated PSA levels with disease prevalence^ of 20%***			***Plain text summary***
						csPrCas undetected (95% CI)	*Unnecessary biopsies avoided (95% CI)*	*NPV*	Using mpMRI with or without PSAD to triage men to biopsy increases the number of clinically significant cancers undetected and the number of unnecessary biopsies avoided when compared to no triage
ISUP Grade ≥ 2	1 (807)	*Sensitivity* Moderate[a] *Specificity* Low[b]	No biopsy if PIRADS 1-3 and PSAD < 0.15 ng/ml²	0.875 (0.84, 0.91)	0.470 (0.42, 0.52)	25 (18, 32)	376 (336, 416)	0.938	If do not biopsy men with a PIRADS of 1-3 who have a PSAD < 0.15 the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant ** and the number of unnecessary biopsies avoided may be moderate#
ISUP Grade ≥ 2	1 (807)	Moderate[a]	No biopsy if PIRADS 1-3 and PSAD < 0.20 ng/ml²	0.829 (0.79, 0.87)	0.602 (0.55, 0.65)	34 (26, 42)	482 (440, 520)	0.934	If do not biopsy men with a PIRADS 1-3 who have a PSAD < 0.20 the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant** and the number of unnecessary biopsies avoided is likely large#.
ISUP Grade ≥ 2	1 (807)	Moderate[a]	No biopsy if PIRADS 1-2 or PIRADS 3 and PSAD < 0.15 ng/ml²	0.811 (0.77, 0.85)	0.631 (0.58, 0.68)	38 (30, 46)	505 (464, 544)	0.930	If do not biopsy men with a PIRADS of 1-2, or men with a PIRADS of 3 and a PSAD < 0.15, the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant** and the

									number of unnecessary biopsies avoided is likely large#
ISUP Grade ≥ 2	1 (807)	*Sensitivity* Low[b] *Specificity* Moderate[a]	No biopsy if PIRADS 1-2 or PIRADS 3 and PSAD < 0.20 ng/ml[2]	0.788 (0.74, 0.83)	0.677 (0.63, 0.72)	42 (34, 52)	542 (504, 576)	0.928	If do not biopsy men with a PIRADS of 1-2, or men with a PIRADS of 3 and a PSAD < 0.20, the number of undetected ISUP Grade ≥ 2 prostate cancers may be clinically unimportant** and the number of unnecessary biopsies avoided is likely large#
ISUP Grade ≥ 2	1 (807)	*Sensitivity* Low[b] *Specificity* Moderate[a]	No biopsy if PIRADS 1-3	0.758 (0.71, 0.80)	0.708 (0.66, 0.75)	48 (40, 58)	566 (528, 600)	0.922	If do not biopsy men biopsy with a PIRADS of 1-3 the number of undetected ISUP Grade ≥ 2 prostate cancer may be clinically unimportant** and the number of unnecessary biopsies avoided is likely large#

CI = confidence interval; csPrCa = clinically significant prostate cancer; ISUP = International Society of Urological Pathology; NPV = negative predictive value; PIRADS = prostate image-reporting and data system

Clinically significant cancers undetected are the number ISUP grade ≥ 2 prostate cancers not detected by the index test (false negatives); this is a non-desirable outcome of mpMRI triage.

Unnecessary biopsies avoided are the number of index test negative (mpMRI ± PSAD results below the specified threshold for biopsy) individuals without ISUP grade ≥ 2 prostate cancers detected (true negatives) for whom it would be acceptable to avoid biopsy; this is a desirable outcome of mpMRI triage.

NPV is the proportion of individuals without ISUP grade ≥ 2 prostate cancers detected (true negatives) among the total number of index test negative individuals. Note this metric is dependent on the underlying outcome prevalence.

^ Implications are calculated for a prevalence of 20% as there are no data on the prevalence of this outcome in populations of individuals with elevated PSA levels in Australia.

*** Using thresholds of 50, 100 and 200 undetected ISUP Grade ≥ 2 prostate cancer/1000 for small (minimal clinically important difference; MCID), moderate and large effects*

 # Using thresholds of 100, 200 and 400 unnecessary biopsies/1000 for small (MCID), moderate and large effects

[a] Serious concerns re selection bias

[b] Serious concerns re selection bias and imprecision

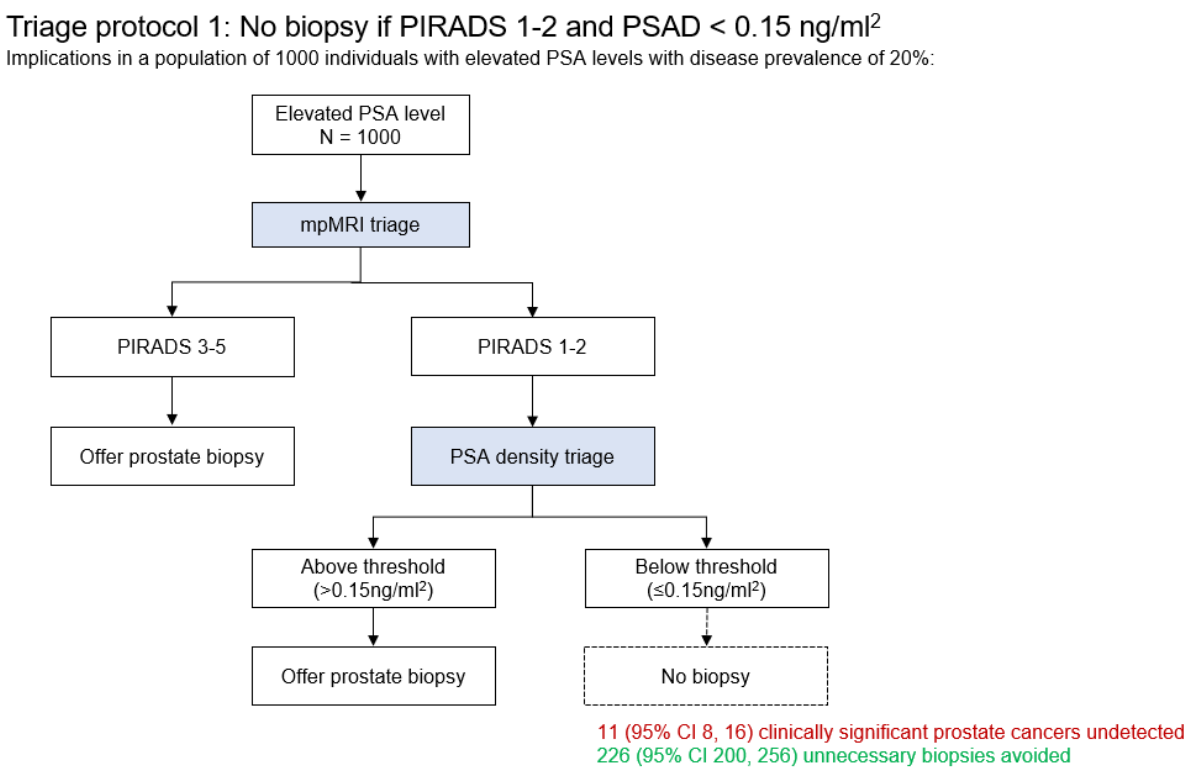

Figure 6. *Flowchart of mpMRI triage protocol 1 summary of findings (Table 8)*

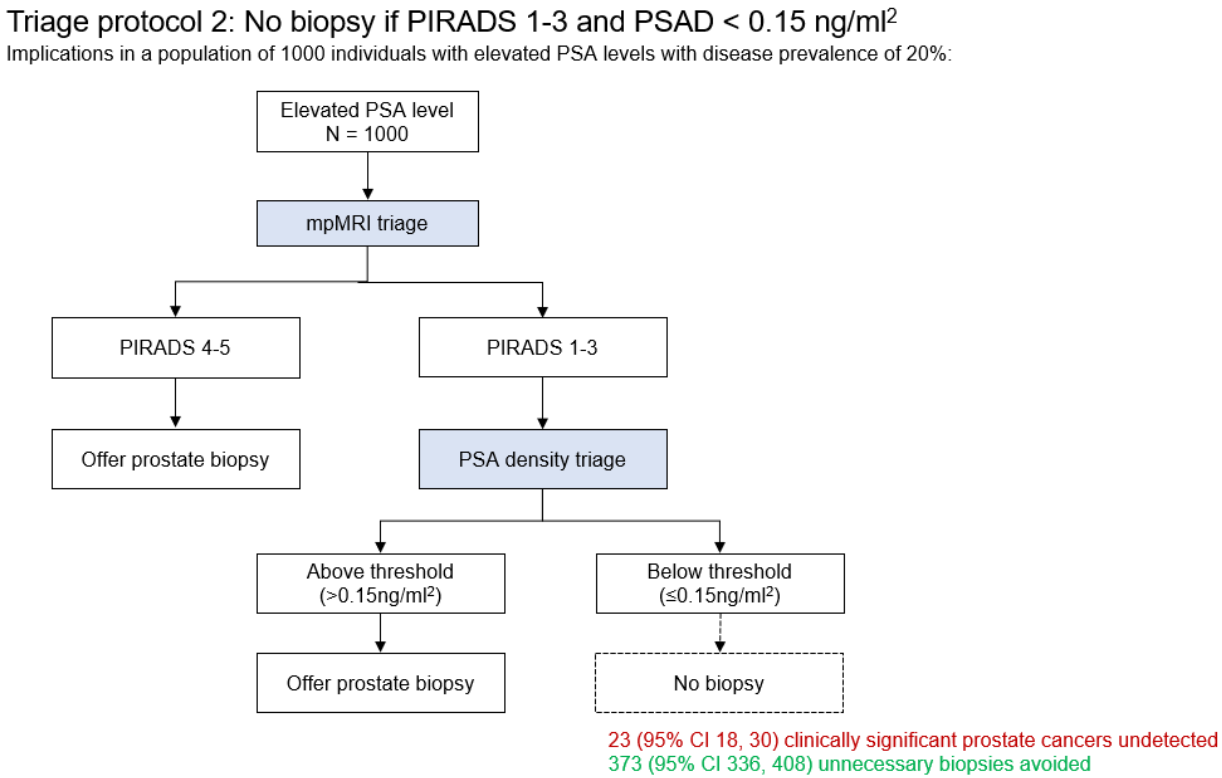

Figure 7. *Flowchart of mpMRI triage protocol 2 summary of findings (Table 8)*

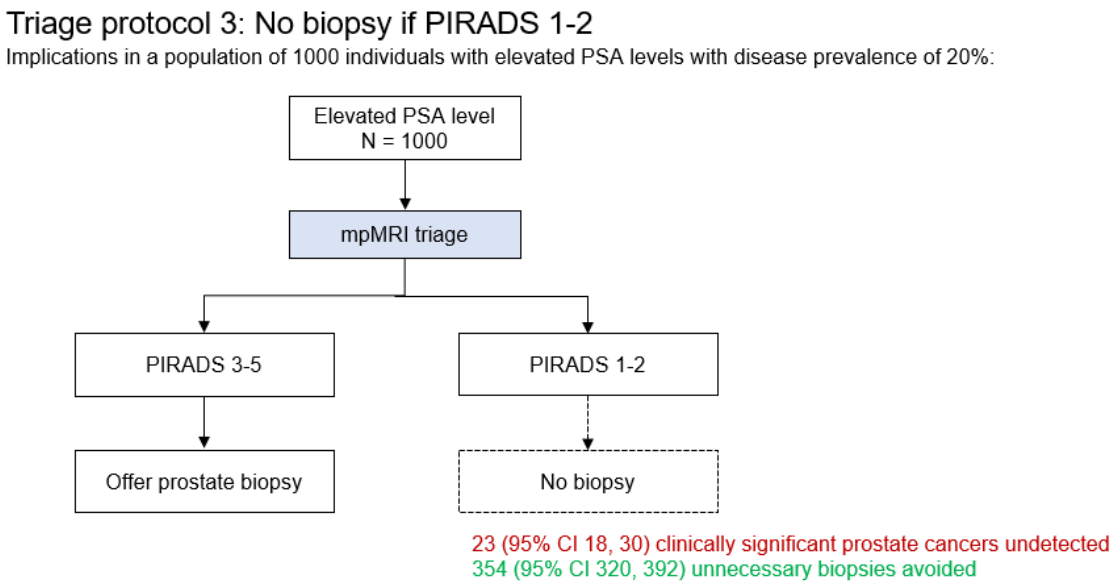

Figure 8. *Flowchart of mpMRI triage protocol 3 summary of findings (Table 8)*

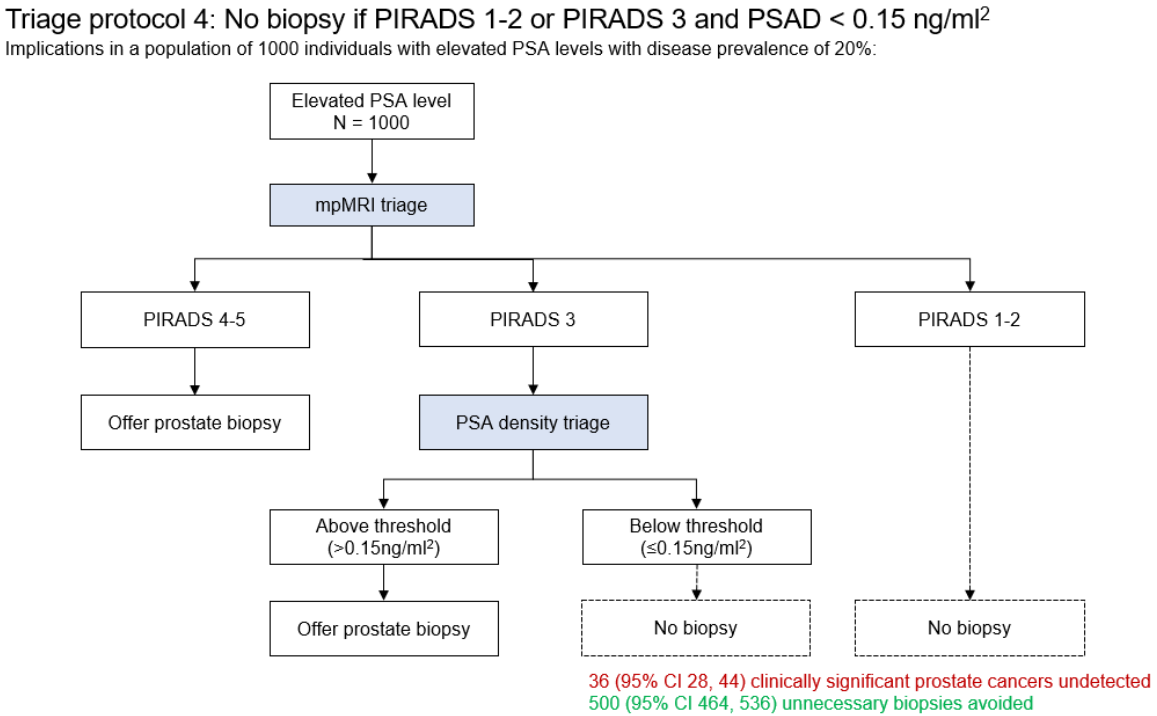

Figure 9. *Flowchart of mpMRI triage protocol 4 summary of findings (Table 8)*

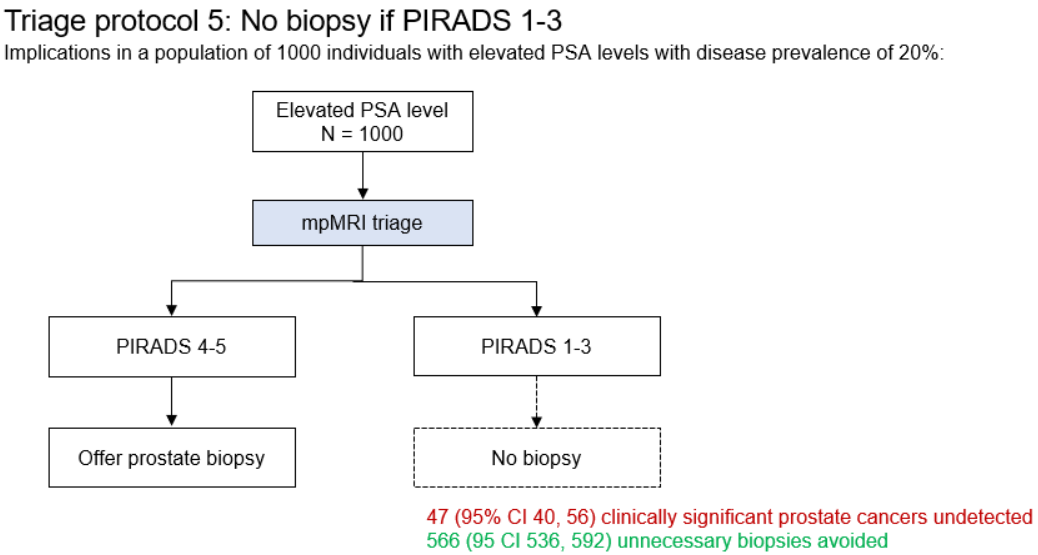

Figure 10. *Flowchart of mpMRI triage protocol 5 summary of findings (Table 8)*

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APPENDICES

Appendix A: Literature search strategies

A.1 Search strategies for systematic reviews published 2010 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2010 -Current"
20	(Systematic* adj3 review*).tw.
21	(meta-analys* or meta analys*).tw.
22	20 or 21
23	19 and 22
24	remove duplicates from 23

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2010 and Jan 2024, in Cochrane Reviews (Word variations have been searched)

A.2 Search strategies for primary studies published 2022 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	prostat* biops*.tw.
5	1 or 2 or 3 or 4
6	multiparametric magnetic resonance imaging/
7	(magnet* adj2 resonance adj2 imag*).tw.
8	"prostate imaging reporting and data system"/
9	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
10	((multiparametric or multi-parametric) adj3 imag*).tw.
11	6 or 7 or 8 or 9 or 10
12	dens*.tw.
13	"PSAD".tw.
14	"PSA-D".tw.
15	12 or 13 or 14
16	5 and 11 and 15
17	limit 16 to english language
18	limit 17 to yr="2022 -Current"
19	conference abstract.pt.
20	18 not 19
21	remove duplicates from 20

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2018 and Jan 2024, in Cochrane Reviews (Word variations have been searched)

Appendix B: GRADE assessment of the certainty of the evidence

Ratings	*Definitions*
⊕⊕⊕⊕ High certainty	The panel is very confident that the true effect lies close to that of the estimate of the effect
⊕⊕⊕◯ Moderate certainty	The panel is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

⊕⊕◯◯ Low certainty	The panel's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕◯◯◯ Very low certainty	The panel has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reported based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Did not directly consider using mpMRI alone or mpMRI in combination with PSA density to triage men to biopsy

Appendix D: Excluded Studies

Article	*DOI/Link*	*Reason for exclusion*
Articles from primary studies search and citation searching		
Abdul Raheem 2023	https://dx.doi.org/10.1080/2090598X.2022.2119711	No relevant reference standard
Alterbeck 2022	https://dx.doi.org/10.1016/j.euf.2022.06.008	No relevant index test
Alterbeck 2023	https://dx.doi.org/10.1111/bju.16143	No relevant index test
Anacleto 2022	https://dx.doi.org/10.4081/aiua.2022.1.32	No relevant reference standard
Aphinives 2023	https://dx.doi.org/10.1186/s12301-023-00335-9	No relevant reference standard
Arafa 2023	https://dx.doi.org/10.4103/sjmms.sjmms_49_23	No relevant reference standard
Arafa 2023	https://dx.doi.org/10.4103/ua.ua_22_22	No relevant reference standard
Arber 2023	https://dx.doi.org/10.1007/s00345-023-04643-1	No relevant population
Arik 2022	https://dx.doi.org/10.56434/j.arch.esp.urol.20227505.60	No relevant reference standard
Arulraj 2024	https://dx.doi.org/10.1016/j.prnil.2024.03.005	No relevant reference standard
Aslanoglu 2024	https://dx.doi.org/10.4274/uob.galenos.2023.2023.6.2	No relevant reference standard
Avolio 2024	https://dx.doi.org/10.5489/cuaj.8675	No relevant reference standard
Bahlburg 2023	https://dx.doi.org/10.1159/000529946	No relevant reference standard
Bittencourt 2022	https://dx.doi.org/10.1007/s00330-021-08407-6	No relevant reference standard
Bogner 2022	https://dx.doi.org/10.1007/s00261-022-03444-1	No relevant population
Bostanci 2024	https://dx.doi.org/10.1016/j.acuroe.2023.10.004	No relevant population
Bratt 2023	https://dx.doi.org/10.1016/j.eururo.2023.11.013	No relevant index test
Cash 2023	https://dx.doi.org/10.1038/s41391-022-00579-6	Excluded publication type
Chang 2024	https://dx.doi.org/10.1097/JCMA.0000000000001117	No relevant population
Chau 2023	https://dx.doi.org/10.1177/20514158211065949	No relevant reference standard
Chen 2022	https://dx.doi.org/10.2217/fon-2021-1538	No relevant population
Chen 2023	https://dx.doi.org/10.4111/icu.20230060	No relevant reference standard
Chiu 2023	https://dx.doi.org/10.1097/JU.0000000000003450	No relevant reference standard
Chiu 2023	https://dx.doi.org/10.4103/UROS.UROS_33_22	No relevant reference standard
Cussenot 2023	https://dx.doi.org/10.1111/bju.15968	No relevant reference standard
Dahl 2024	https://dx.doi.org/10.1016/j.urolonc.2023.11.004	No relevant population
Davik 2023	https://dx.doi.org/10.1111/bju.16163	No relevant reference standard
de Oliveira Correia 2024	https://dx.doi.org/10.2214/AJR.23.30611	No relevant reference standard
Eldred-Evans 2023	https://dx.doi.org/10.1111/bju.15899	No relevant reference standard

Feng 2024	https://dx.doi.org/10.1186/s12894-024-01411-0	No relevant reference standard
Feng 2024	https://dx.doi.org/10.2147/CMAR.S476636	No relevant reference standard
Frisbie 2023	https://dx.doi.org/10.1038/s41391-022-00549-y	No relevant reference standard
Girometti 2022	https://dx.doi.org/10.1259/bjr.20210886	No relevant reference standard
Girometti 2023	https://dx.doi.org/10.1016/j.ejrad.2023.110897	No relevant reference standard
Gold 2023	https://dx.doi.org/10.1016/j.urology.2023.05.003	No relevant reference standard
Guo 2023	https://dx.doi.org/10.1038/s41391-023-00782-z	No relevant reference standard
Guo 2024	https://dx.doi.org/10.1038/s41391-023-00782-z	No relevant population
Haj-Mirzaian 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.4258	No relevant reference standard
Hamm 2024	https://dx.doi.org/10.1007/s00330-024-10700-z	No relevant reference standard
Haroon 2022	https://dx.doi.org/10.5489/cuaj.7455	No relevant population
Hruba 2024	https://dx.doi.org/10.1007/s11845-024-03771-w	No relevant population
Israel 2022	https://dx.doi.org/10.1111/bju.15562	No relevant reference standard
Karami 2023	https://dx.doi.org/10.5812/ijcm-132340	No relevant population
Kaufmann 2022	https://dx.doi.org/10.1002/pros.24286	No relevant population
Kim 2023	https://dx.doi.org/10.1016/j.prnil.2023.07.001	No relevant reference standard
Kong 2023	https://dx.doi.org/10.1177/20514158211065946	No relevant reference standard
Lei 2022	https://dx.doi.org/10.3389/fonc.2022.992032	No relevant reference standard
Lin 2023	https://dx.doi.org/10.1007/s11255-023-03692-0	Excluded study design
Lophatananon 2023	https://dx.doi.org/10.1177/20514158211059057	No relevant reference standard
Malshy 2024	https://dx.doi.org/10.1002/pros.24757	No relevant reference standard
Mian 2024	https://dx.doi.org/10.1097/JU.0000000000003979	Excluded study design
Morote 2022	https://dx.doi.org/10.1177/03936155221081537	No relevant reference standard
Oderda 2024	https://dx.doi.org/10.3390/curroncol31070308	No relevant population
Pellegrino 2023	https://dx.doi.org/10.1016/j.euf.2022.10.002	Excluded study design
Rajendran 2024	https://dx.doi.org/10.1093/bjr/tqad027	No relevant reference standard
Ren 2024	https://dx.doi.org/10.3389/fonc.2024.1413953	No relevant reference standard
Sahin 2024	https://dx.doi.org/10.1016/j.prnil.2024.06.001	No relevant population
Siddiqui 2023	https://dx.doi.org/10.1038/s41391-023-00660-8	No relevant reference standard
Steuber 2022	https://dx.doi.org/10.1016/j.euo.2020.12.003	No relevant reference standard
Tezcan 2023	https://dx.doi.org/10.5152/tud.2023.220199	No relevant reference standard
Tosoian 2022	https://dx.doi.org/10.1016/j.urology.2021.11.033	No relevant reference standard
Wagaskar 2022	https://dx.doi.org/10.22037/uj.v18i.6852	No relevant reference standard
Wang 2022	https://dx.doi.org/10.3389/fonc.2022.1024204	No relevant reference standard
Wang 2023	https://dx.doi.org/10.1007/s11255-023-03631-z	No relevant reference standard
Wang 2023	https://dx.doi.org/10.1016/j.euo.2023.08.002	No relevant reference standard
Wang 2024	https://dx.doi.org/10.21037/qims-23-875	No relevant reference standard
Wei 2022	https://dx.doi.org/10.1007/s00261-022-03592-4	No relevant reference standard
Wen 2022	https://dx.doi.org/10.3389/fonc.2022.861928	No relevant reference standard
Wen 2024	https://dx.doi.org/10.1038/s41598-024-57337-y	No relevant reference standard
Ye 2024	https://dx.doi.org/10.1016/j.euros.2024.04.001	No relevant reference standard
Zhang 2023	https://dx.doi.org/10.4103/aja202288	No relevant reference standard
Zhou 2023	https://dx.doi.org/10.3390/jcm12010339	No relevant reference standard
Articles from Wang 2024 and Drost 2019 systematic reviews		

Abd-Alazeez 2014	https://doi.org/10.1016%2Fj.urolonc.2013.06.007	No relevant population
Abdi 2015	https://doi.org/10.1016/j.urolonc.2015.01.004	No relevant population
Ahmed 2017	https://doi.org/10.1016/s0140-6736(16)32401-1	No relevant index test
Avolio 2021	https://doi.org/10.1016/j.urolonc.2021.05.030	No relevant population
Bertolo 2021	https://doi.org/10.1016/j.purol.2020.12.008	No relevant reference standard
Boesen 2019	https://doi.org/10.1016/j.euo.2018.09.001	No relevant index test
Borkowetz 2019	https://doi.org/10.1159/000492495	No relevant population
Buisset 2021	https://doi.org/10.1097/JU.0000000000001414	No relevant reference standard
Cuocolo 2018	https://doi.org/10.1016/j.ejrad.2018.05.004	No relevant index test
Dal Moro 2019	https://doi.org/10.1007/s40520-018-0939-4	No relevant population
Deniffel 2020	https://doi.org/10.1097/JU.0000000000000518	No relevant population
Deniffel 2021	https://doi.org/10.1148/radiol.2021204112	No relevant population
Distler 2017	https://doi.org/10.1016/j.juro.2017.03.130	No relevant population
Elkhoury 2019	https://doi.org/10.1001/jamasurg.2019.1734	No relevant reference standard
Falagario 2020	https://doi.org/10.1016/j.euo.2019.08.015	No relevant reference standard
Falagario 2021	https://doi.org/10.1016/j.euo.2020.08.014	No relevant reference standard
Fascelli 2016	https://doi.org/10.1016/j.urology.2015.09.035	No relevant population
Gan 2022	https://doi.org/10.2214/AJR.21.26569	No relevant population
Girometti 2022	https://doi.org/10.1259%2Fbjr.20210886	No relevant reference standard
Godtman 2024	https://doi.org/10.1016/j.euo.2023.11.003	No relevant outcome
Gortz 2021	https://doi.org/10.1016/j.euf.2019.11.012	No relevant population
Grey 2015	https://doi.org/10.1111/bju.12862	No relevant index test
Hansen 2016	https://doi.org/10.1016/j.eururo.2016.02.064	Overlapping data
Hansen 2017	https://doi.org/10.1111/bju.14049	No relevant population
Hansen 2017	https://doi.org/10.1111/bju.13711	No relevant population
Kaufmann 2022	https://doi.org/10.1002/pros.24286	No relevant outcome
Kesch 2017	https://doi.org/10.1159/000458764	No relevant population
Kim 2020	https://doi.org/10.1186/s12916-020-01548-3	No relevant reference standard
Kim 2020	https://doi.org/10.1111/iju.14213	No relevant reference standard
Kim 2021	https://doi.org/10.1007/s00345-020-03352-3	No relevant population
Kinnaird 2020	https://doi.org/10.1097/JU.0000000000001232	No relevant population
Knaapila 2020	https://doi.org/10.1016/j.euo.2019.08.008	No relevant index test
Lawrence 2014	https://doi.org/10.1007/s00330-014-3159-0	No relevant population
Liang 2021	https://doi.org/10.1038/s41598-021-83802-z	No relevant index test
Lim 2021	https://doi.org/10.5489/cuaj.6781	No relevant population
Lophatananon 2021	https://doi.org/10.1177/20514158211059057	No relevant reference standard
Mortezavi 2018	https://doi.org/10.1016/j.juro.2018.02.067	No relevant index test
Muthuveloe 2016	https://doi.org/10.5173/ceju.2016.675	No relevant index test
Nafie 2014	https://doi.org/10.1038/pcan.2014.4	No relevant index test
Nafie 2017	https://pubmed.ncbi.nlm.nih.gov/28299763/	No relevant population
Niu 2017	https://doi.org/10.1186/s12880-017-0184-x	No relevant reference standard
Oishi 2019	https://doi.org/10.1016/j.juro.2018.08.046	No relevant population
Pan 2021	https://doi.org/10.3389/fonc.2021.740868	No relevant index test
Pepe 2013	https://pubmed.ncbi.nlm.nih.gov/23482802/	No relevant population

Peters 2022	https://doi.org/10.1016/j.eururo.2022.07.022	No relevant population
Ploussard 2014	https://doi.org/10.1016/j.eururo.2012.05.049	No relevant index test
Radtke 2017	https://doi.org/10.1016/j.eururo.2017.03.039	No relevant population
Russo 2021	https://doi.org/10.1016/j.euo.2021.03.007	No relevant reference standard
Schoots 2021	https://doi.org/10.1111/bju.15277	Superseded
Sekito 2021	https://doi.org/10.21873/anticanres.14992	No relevant index test
Sokhi 2020	https://doi.org/10.1016/j.crad.2020.08.011	No relevant reference standard
Stanzione 2021	https://doi.org/10.1016/j.acra.2020.05.014	No relevant reference standard
Stevens 2020	https://doi.org/10.1016/j.urolonc.2020.05.024	No relevant reference standard
Stonier 2021	https://doi.org/10.1016/j.euf.2020.09.012	No relevant reference standard
Takeshima 2020	https://doi.org/10.1007/s11255-020-02533-8	No relevant population
Thompson 2014	https://doi.org/10.1016/J.JURO.2014.01.014	No relevant index test
Thompson 2016	https://doi.org/10.1016/j.juro.2015.10.140	No relevant reference standard
Tsivian 2017	https://doi.org/10.1111/iju.13251	No relevant population
van Leeuwen 2017	https://doi.org/10.1111/bju.13814	No relevant index test
Washino 2017	https://doi.org/10.1111/bju.13465	No relevant reference standard
Yu 2021	https://doi.org/10.2147/CMAR.S318404	No relevant population
Zhang 2020	https://doi.org/10.1016/j.clgc.2019.11.011	No relevant population
Zhang 2020	https://doi.org/10.1007/s10147-019-01524-9	No relevant population
Zheng 2021	https://doi.org/10.1002/jmri.27793	No relevant population

Appendix E: Supplementary material

*Table S1. Summary of findings for **the difference** in clinically significant cancer detected and unnecessary biopsies if the decision to biopsy takes into account PSA density as well as mpMRI results, if the prevalence amongst men with elevated PSA levels of ISUP Grade ≥ 2 prostate cancer is 10%, 20% or 30%*

Outcome	Studies (Participants)	Certainty of the evidence (GRADE)	Control threshold for biopsy	Control summary sensitivity	Control summary specificity	Relative sensitivity (95% CI)	Relative specificity (95% CI)	Implications in a population of 1000 individuals with elevated PSA levels with disease prevalence^ of:						Plain text summary^^
								10%		20%		30%		
								Additional csPrCas detected by PSAD (95% CI)	Additional unnecessary biopsies (95% CI)	Additional csPrCas detected by PSAD (95% CI)	Additional unnecessary biopsies (95% CI)	Additional csPrCas detected by PSAD (95% CI)	Additional unnecessary biopsies (95% CI)	Adding PSAD to mpMRI for triage to biopsy increases the number of clinically significant cancers detected and the number of unnecessary biopsies
***For PIRADS 1-2*: No biopsy if PSAD < 0.15* ng/ml² vs No biopsy**														
ISUP Grade ≥ 2	2 (947)	*Sensitivity* High *Specificity* Moderate[a]	PIRADS ≥ 3	0.884	0.443	1.07 (1.03, 1.12)	0.64 (0.54, 0.76)	7 (3, 11)	143 (96, 184)	12 (5, 21)	127 (84, 163)	19 (8, 32)	111 (74, 143)	For individuals with a PIRADS of 1-2, if only those with a PSAD < 0.15 rather than all **do not undergo biopsy**, there will be a clinically unimportant** increase in detected ISUP Grade ≥ 2 prostate cancer and a likely small increase in unnecessary biopsies#.
***For PIRADS 1-2: No biopsy if PSAD ≤ 0.20* ng/ml² vs No biopsy**														
ISUP Grade ≥ 2	1 (807)	*Sensitivity* High *Specificity* Moderate[a]	PIRADS ≥ 3	0.878	0.453	1.05 (1.00, 1.10)	0.84 (0.71, 0.98)	4 (0, 9)	65 (8, 118)	9 (0, 18)	58 (7, 105)	13 (0, 26)	51 (6, 92)	For individuals with a PIRADS of 1-2, if only those with a PSAD ≤ 0.20 rather than all **do not undergo biopsy**, there will be a clinically unimportant** increase in detected ISUP Grade ≥ 2 prostate cancer and a likely clinically unimportant increase in unnecessary biopsies#.
***For PIRADS 1-3: No biopsy if PSAD < 0.15* ng/ml² vs No biopsy**														
ISUP Grade ≥ 2	2 (947)	*Sensitivity* High *Specificity* Moderate[a]	PIRADS ≥ 4	0.766	0.707	1.15 (1.08, 1.23)	0.66 (0.59, 0.73)	11 (6, 17)	216 (172, 261)	23 (12, 35)	192 (153, 232)	34 (18, 53)	168 (134, 203)	For individuals with a PIRADS of 1-3, if only those with a PSAD < 0.15 rather than all **do not undergo biopsy**, there will be a clinically unimportant** increase in detected ISUP Grade ≥ 2 prostate cancer and a likely small increase in unnecessary biopsies#.
***For PIRADS 1-3: No biopsy if PSAD ≤ 0.20* ng/ml² vs No biopsy**														
ISUP Grade ≥ 2	1 (807)	*Sensitivity* High *Specificity* Moderate[a]	PIRADS ≥ 4	0.758	0.708	1.09 (1.02, 1.18)	0.85 (0.77, 0.94)	7 (2, 14)	96 (38, 147)	14 (3, 27)	85 (34, 130)	21 (5, 42)	74 (30, 114)	For individuals with a PIRADS of 1-3, if those with a PSAD ≤ 0.20 rather than all **do not undergo biopsy**, there will be a clinically unimportant** increase in detected ISUP Grade ≥ 2 prostate cancer and a likely clinically

														unimportant increase in unnecessary biopsies#.
For PIRADS 3:* No biopsy if PSAD < 0.15 *ng/ml²* *vs* **No biopsy**														
ISUP Grade ≥ 2	2 (947)	*Sensitivity* High *Specificity* Moderate[a]	PIRADS ≥ 4	0.766	0.707	1.07 (1.00, 1.15)	0.88 (0.81, 0.97)	5 (0, 11)	76 (19, 120)	11 (0, 23)	68 (17, 108)	16 (0, 34)	60 (15, 94)	For individuals with a PIRADS of 3, if those with a PSAD < 0.15 rather than all **do not undergo biopsy,** there will be a clinically unimportant** increase in detected ISUP Grade ≥ 2 prostate cancer and a likely clinically unimportant increase in unnecessary biopsies#.
***For PIRADS 3:* No biopsy if PSAD ≤ 0.20** *ng/ml²* *vs* **No biopsy**														
ISUP Grade ≥ 2	1 (807)	*Sensitivity* Moderate[a] *Specificity* Moderate[a]	PIRADS ≥ 4	0.758	0.708	1.04 (0.96, 1.12)	0.96 (0.87, 1.05)	3 more (3 less, 9 more)	26 more (32 less, 83 more)	6 more (6 less, 18 more)	23 more (28 less, 74 more)	9 more (9 less, 28 more)	20 more (25 less, 64 more)	For individuals with a PIRADS of 3, if those with a PSAD ≤ 0.20 rather than all **do not undergo biopsy** there will likely be a clinically unimportant increase in detected ISUP Grade ≥ 2 prostate cancer** and unnecessary biopsies#.

CI = confidence interval; csPrCa = clinically significant prostate cancer; ISUP = International Society of Urological Pathology; PIRADS = prostate image-reporting and data system
Additional clinically significant cancers detected are the number of additional ISUP grade ≥ 2 prostate cancers detected if PSAD is used in addition to mpMRI to triage men to biopsy; this is a desirable outcome of using in PSAD in addition to mpMRI to triage men to biopsy.
Additional unnecessary biopsies are the number of additional unnecessary biopsies if PSAD is used in addition to mpMRI to triage men to biopsy; this is a non-desirable outcome of using in PSAD in addition to mpMRI to triage men to biopsy.
^ Implications are calculated for a range of prevalences as there are no data on the prevalence of this outcome in populations of individuals with elevated PSA levels in Australia.
^^ If prevalence of ISUP Grade ≥ 2 prostate cancer for men with elevated PSA levels is 20%
*** Using thresholds of 50, 100 and 200 detected ISUP Grade ≥ 2 prostate cancer/1000 for small (minimal clinically important difference; MCID), moderate and large effects*
 # Using thresholds of 100, 200 and 400 unnecessary biopsies/1000 for small (MCID), moderate and large effects
** PSAD ≤ 0.15 in one study and < 0.15 in the other study*
[a] Serious concerns re imprecision

3.10 Clinical question 8 – Prostate Biopsy PICO 8A

Clinical question: *For biopsy naïve men with a PI-RADS 4 or 5 lesion on multiparametric MRI (mpMRI) are targeted biopsies alone acceptable/ reasonable/ adequate? (is a systematic biopsy necessary?)*

Introduction

This is the first of three systematic reviews which address Clinical question 8.

Systematic review report for PICO 8A: Comparisons of prostate cancer detection by mpMRI targeted biopsy compared to combined systematic and targeted biopsy

Authors

Chelsea Carle, Karen Chiam, Susan Yuill, Michael David, Suzanne Hughes

PICO

This systematic review addresses the following PICO which is summarised in detail in Table 1.

PICO 8A. *For biopsy naïve men with a PI-RADS 4 or 5 lesion on mpMRI how do the rates of clinically significant and insignificant cancers detected using a targeted biopsy alone compare with those using a targeted biopsy together with a 20 or more-core systematic biopsy?*

Table 1. *PICO components*

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Biopsy naïve individuals with a PI-RADS 4-5 lesion on mpMRI	MRI-targeted biopsy only	≥ 20 core systematic biopsy +/- MRI-targeted biopsy	Detection of • ≥ ISUP grade 2 prostate cancer • ISUP grade 1 prostate cancer • ≥ ISUP grade 3 prostate cancer	Randomised controlled trial or Fully paired comparison

ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PI-RADS = Prostate Image-Reporting and Data System

1. Methods

1.1 Selection criteria

Table 2. *Selection criteria*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	
Study design	Cross-sectional head-to-head (fully paired) studies, or Randomised controlled trials or Systematic reviews thereof	
Population	Biopsy naïve individuals with a PI-RADS or Likert score 4-5 lesion on mpMRI	> 10% of population have undergone prior biopsy and outcomes not stratified for biopsy-naïve patients. Prostate cancer patients (restricted to radical prostatectomy specimens) Not 5-point Likert scale.
Intervention	**MRI-targeted biopsy only** • minimum 2-cores, • any fusion method (software registration, cognitive, in-bore) • transperineal or transrectal approach	Single core targeted biopsy Perilesional biopsies
Comparator	≥ 20 core systematic biopsy • includes template biopsies, • transperineal or transrectal approach +/- MRI-targeted biopsy	Systematic or template biopsy < 20 cores. Systematic biopsy excludes regions sampled by targeted biopsy Biopsy approach differed from that used for the intervention
Outcome	Detection of: **ISUP grade ≥ 2 (primary outcome)**, or ISUP grade ≥ 3, or ISUP grade 1	ISUP grade ≥ 2 combined with a subgroup of ISUP grade 1 for example • Max CCL ≥5 mm for Gleason score 6 disease
Analyses	Per-patient	Per-lesion
Publication date	From 2010 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

CCL = cancer core length; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PI-RADS = Prostate Image-Reporting and Data System

1.2 Definitions and terminology

For the purposes of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).

ISUP grade ≥ 3 prostate cancer is prostate cancer scored as Gleason Score 7(4+3) or higher on histopathological findings (Epstein 2016).

ISUP grade 1 prostate cancer is prostate cancer scored as Gleason Score 6(3+3) on histopathological findings (Epstein 2016).

Multi-parametric MRI (mpMRI) refers to an imaging protocol used to detect and characterise tissue abnormalities to determine the presence and severity of cancer. Prostate mpMRI acquisition includes T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging.
Systematic biopsy refers to a biopsy in which cores are taken from all areas of the prostate according to a template or pattern and includes saturation biopsies.
Targeted biopsy refers to a biopsy in which cores are taken from lesions identified on MRI as suspicious of harbouring significant cancer. Cognitive, software registration or in-bore image fusion techniques are used to identify lesions for biopsy.

- Cognitive image fusion refers to the operator visually fusing MRI images and real time ultrasound pictures.
- Software registration image fusion refers to using software to fuse uploaded MRI images to real time ultrasound.
- In-bore image fusion refers to fusing prior MRI images and a real time MRI during biopsy.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website

- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and as the evidence for mpMRI-targeted biopsy continues to evolve, be based on literature published up until 2022 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

A search for systematic reviews of prostate mpMRI published from 2010 onwards in Medline, Embase and Cochrane Systematic Review databases (search strategy in Appendix A) yielded 302 records. Two relevant systematic reviews were identified:

- Haider et al (2021), a systematic review for the Cancer Care Ontario Guideline 27-2 Version 2: *Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer*, captured relevant literature published from 1st May 2013 to 1st September 2020
- Drost et al (2019) captured relevant literature published from 1st January 1990 to 31st July 2018

We assessed studies included in the Haider 2021 and Drost 2019 systematic reviews for inclusion in our systematic review, and designed separate searches to identify randomised controlled trials and head-to-head (paired) studies or systematic reviews thereof published from 2018 onwards. Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations), Embase and Cochrane CENTRAL databases were searched initially on 6th December 2023 combining text terms and database-specific subject headings

for prostate cancer, multiparametric MRI and biopsy, and a filter for randomised controlled trials (RCT / CCT - MEDLINE, Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 2024-07-30.)

Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st November 2024. The searches were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the searches is included as Appendix A. Reference lists of recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

The following study characteristics were extracted: Country and year of publication, study setting and period, participant eligibility and age, details of mpMRI, MRI-targeted biopsy and systematic biopsy, and relevant outcomes reported. Cancer undetected by MRI-targeted biopsy, and relative detection of MRI-targeted biopsy compared to combined systematic and MRI-targeted biopsy were calculated. Pooled analyses were planned where there were two or more studies reporting the same outcome. The *meta* command in Stata Version 18.0 (StataCorp 2023) was used to generate study-specific and pooled relative sensitivity of MRI-targeted biopsy compared to combined systematic and MRI-targeted biopsy to detect clinically significant prostate cancer, and associated 95% confidence intervals, using a Tukey-Freeman proportion random-effects model. Sensitivity analysis using the *leaveoneout* command were planned for outlying study estimates. Forest plots were obtained to present the results graphically.

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias of outcomes in each included study, with independent third-reviewer adjudication as needed. For randomised studies, risk of bias assessment was planned using the Cochrane Collaboration Risk of Bias-II tool (Sterne 2019), and for head-to-head (paired) studies, using a modified version of the Quality of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool (Whiting 2011). The overall risk of bias of studies was rated low, moderate, high or unclear.

1.7 GRADE assessment of the certainty of the evidence

GRADE assessments were planned to assess the certainty of the body of evidence for each outcome. (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence was rated *high*, *moderate*, *low* or *very low* based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Schunemann 2013), Schunemann 2020a, Schuneman 2020b and Schunemann et al 2022. Imprecision was assessed in the context of whether there was a clinically important decrease using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. These thresholds were predetermined by the Biopsy Working Group following GRADE guidance provided by Schunemann 2022. Potential publication bias (or small study effects) was assessed using a Funnel Plot if 10 or more studies. Where there were less than 10 studies: for randomised evidence, clinical trial registries were searched for potentially relevant trials (see Section 1.8 below for search details) that had

planned completion dates prior to 2020 (5 or more years ago), that had not been terminated and for which results had not been published suggesting publication bias; and for evidence from fully paired studies sources of funding and conflicts of interest were considered. As per GRADE guidance, studies started with a high level of certainty in the evidence and downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

1.8 Clinical trial registry searches

Potentially relevant ongoing and unpublished trials were identified from literature and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 29 October 2024. The clinical trial registries were searched with the search terms listed below:

Clinicaltrials.gov using the terms:

"prostate cancer" and "multiparametric MRI" and "biopsy"

"prostate cancer" and "MRI" and "biopsy"

"prostate cancer" and "magnetic resonance imaging" and "biopsy"

International Clinical Trials Registry Platform using the terms:

"prostate cancer" and "multiparametric MRI" and "biopsy"

"prostate cancer" and "MRI" and "biopsy"

"prostate cancer" and "magnetic resonance imaging" and "biopsy"

Australia and New Zealand Clinical Trial Registry using the terms:

"prostate cancer" and "magnetic resonance imaging"

"prostate cancer" and "multiparametric MRI"

"prostate cancer" and "MRI"

"prostate cancer" and "biopsy"

2. Results

2.1 Guidelines searches

One potentially relevant guideline was identified which was based on systematic reviews of the literature published up until 2022 or later. It was not considered for adoption as the systematic reviews were not accessible (Appendix C).

2.2 Literature searches

The systematic search for studies published from 2018 onwards identified 5908 unique records to November 1st, 2024 (Figure 1). Of these, 284 full text articles were retrieved for a more detailed evaluation. 36 studies published to 2020 included in the Haider 2021 and Drost 2019 systematic reviews, and one article identified in a reference list were also assessed for inclusion. Three head-to-head studies met criteria for inclusion in our systematic review: Hansen 2018, Mortezavi 2018, and Bonekamp 2019. No randomised controlled trials met

inclusion criteria. There were no studies that included Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.

The retrieved articles that were not included in this systematic review and the reasons for their exclusion are documented in Appendix D. The main reasons for exclusion were irrelevant comparator or irrelevant population.

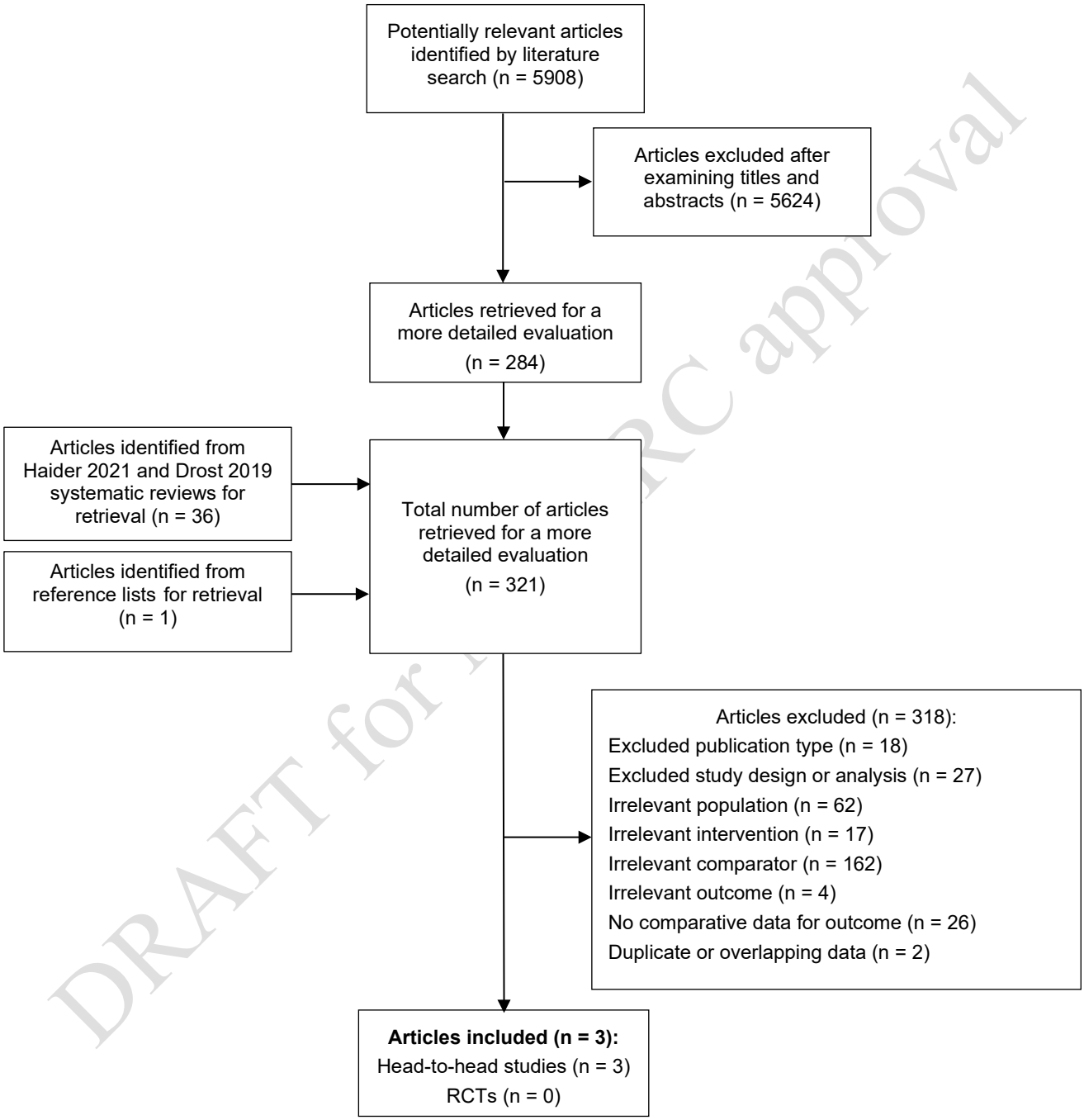

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

2.3 Characteristics of included studies

Table 3. *Study characteristics of included head-to-head (paired) studies reporting detection of clinically significant prostate cancer by multiparametric MRI-targeted biopsy alone compared to combined systematic and MRI-targeted biopsy in biopsy-naïve men with mpMRI score 4-5 lesion*

Study	*Setting and study period*	*Population*	*mpMRI*	*mpMRI-Targeted biopsy (TB)*	*Systematic biopsy (SB)*	*Combined biopsy (SB + TB)*	*Outcomes of interest*
Hansen 2018 Germany, United Kingdom, Australia Prospective	Three tertiary centres 2012-2016	Men aged <80 years with mpMRI score 4-5 lesion (PIRADS v1 pre-2015 or v2 2015 onwards) undergoing TB + SB N = 370 Biopsy naïve: 100% Age mean: NR PSA level mean: NR	Read by radiologists with team-based peer-review of images in equivocal cases and ongoing histological feedback on >150 MRI/year	Transperineal TRUS-Fusion TB (2 centres) or Cognitive TB (1 centre) prior to SB ≥2 cores per lesion Median (IQR) 4 (2-5) cores per patient^	Transperineal Ginsburg protocol: 3-4 cores per each of 6 prostate sectors using 5mm brachytherapy grid	SB + TB Median (IQR) 26 (24-28) cores per patient^	ISUP Grade ≥ 2 *Reported as Gleason Score*
Mortezavi 2018 Switzerland Retrospective	Single tertiary centre 2014-2016	Men with mpMRI score 4-5 lesion (5-point Likert scale) undergoing TB + SB N = 78 Biopsy naïve: 100% Age mean: NR PSA level mean: NR	Read by board certified radiologists (number and experience NR)	Transperineal TRUS-Fusion TB After SB 2-4 cores per lesion Median (IQR) 3 (2-4) cores per patient^	Transperineal template saturation biopsy according to Barzell zones (20 zones) Median (range) 40 (30-55) cores per patient^	SB + TB Total cores per patient NR	ISUP Grade ≥ 2 *Reported as Gleason Score*
Bonekamp 2019 Germany Retrospective	Single research centre 2015-2016	Men with mpMRI score 4-5 lesion (PIRADS v2) undergoing TB + SB N = 111 Biopsy naïve: 100% Age mean: NR PSA level mean: NR	Read by 8 board certified radiologists; 98% read by 7 radiologists with > 3 years of experience in prostate MR image interpretation	Transperineal TRUS-Fusion TB Prior to SB Median (range) 4 (3-5) cores per lesion^	Transperineal biopsy (Ginsburg protocol) Median (range) 23 (20-26) cores per patient^	SB + TB Median (range) 29 (24-33) cores per patient^	ISUP Grade ≥ 2 ISUP Grade ≥ 3 *Reported as Gleason Score*

ISUP = International Society of Urological Pathology; IQR = interquartile range; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; N = number; NR = not reported; PIRADS = Prostate Imaging Reporting and Data System; SB = systematic biopsy; TB = targeted biopsy; TRUS = transrectal ultrasound-guided; v = version
^ Median biopsy cores for overall population with mpMRI score 3-5

2.4 Results by outcome of interest

Clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) – results are shown in Table 4, and Figures 2 and 3

ISUP grade ≥ 3 prostate cancer – results are shown in Table 5

ISUP grade 1 prostate cancer – no results

*1. Results for the detection of **clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer)***

Table 4. *Detection of **clinically significant prostate cancer** (ISUP grade ≥ 2 prostate cancer) by MRI-targeted biopsy alone compared to combined systematic and MRI-targeted biopsy in biopsy-naïve men with mpMRI score 4-5 lesion*

Study	***N***	***csPrCa detected (n)***		***csPrCa undetected if perform TB only***	***Relative sensitivity of TB*** (95% CI)	***csPrCa prevalence***	***Undetected csPrCa per 1000 for a prevalence of 70%*** (95%CI)
		TB	***SB + TB***				
Hansen 2018	370	220	264	44	0.833 (0.79, 0.88)	71.4%	119 (84-147)
Mortezavi 2018	78	36	57	21	0.632 (0.50, 0.75)	73.1%	259 (175-350)
Bonekamp 2019	111	28*	69*	41*	0.406 (0.29, 0.52)	62.2%	413 (336-497)

CI = confidence interval; csPrCa = clinically significant prostate cancer; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; N = number; SB = systematic biopsy; TB = targeted biopsy
** Results reported for cancers detected in the MRI-positive area rather than for targeted biopsies*

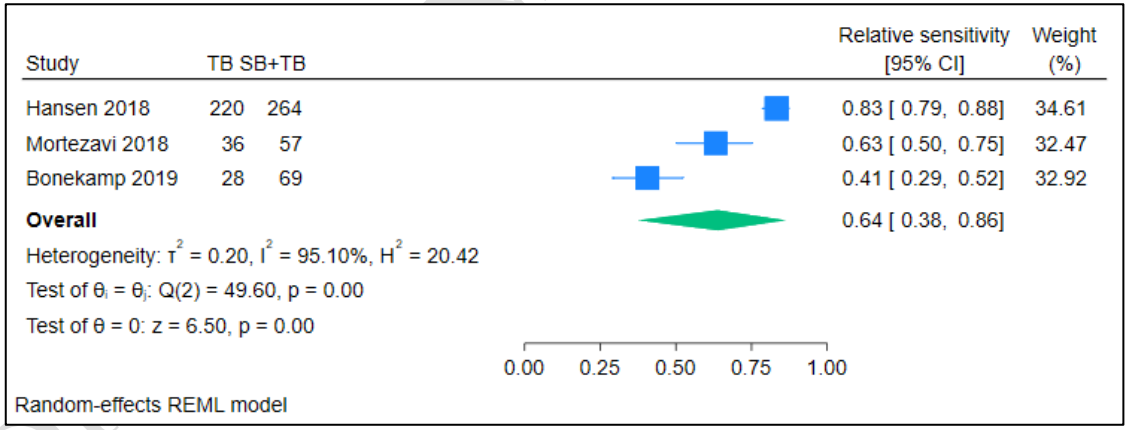

Figure 2. *Forest plot of the sensitivity of MRI-targeted biopsy (TB) relative to combined systematic and MRI-targeted biopsy (SB + TB) for the detection of clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) in biopsy-naïve men with mpMRI score 4-5 lesion. REML = restricted maximum likelihood.*

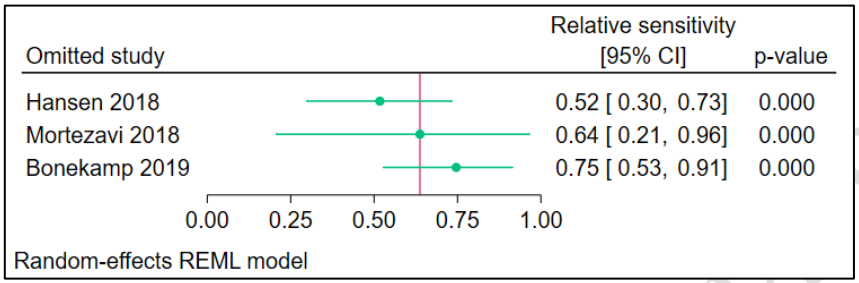

Figure 3. *Forest plot of sensitivity analysis results using the leave-one-out method to show impact of each study on pooled sensitivity of MRI-targeted biopsy relative to combined systematic and MRI-targeted biopsy for the detection of clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) in biopsy-naïve men with mpMRI score 4-5 lesion. REML = restricted maximum likelihood.*

*2. Results for the detection of **ISUP grade ≥ 3 prostate cancer***

Table 5. *Detection of ISUP grade ≥ 3 prostate cancer by MRI-targeted biopsy alone compared to combined systematic and MRI-targeted biopsy in biopsy-naïve men with mpMRI score 4-5 lesion*

Study	***N***	***ISUP ≥3 detected (n)***		***ISUP ≥3 undetected if perform TB only***	***Relative sensitivity of TB*** (95% CI)	***ISUP ≥3 prevalence***
		TB	***SB + TB***			
Bonekamp 2019	111	13*	31*	18*	0.419 (0.25, 0.60)	27.9%

CI = confidence interval; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; N = number; SB = systematic biopsy; TB = targeted biopsy
** Results reported for cancers detected in the MRI-positive area rather than for targeted biopsies*

2.5 Risk of bias

The results of the risk of bias assessments for the included studies are shown in Table 6.

Table 6. *Risk of bias assessments for included head-to-head (paired) studies using a modified version of the Quality of Diagnostic Accuracy Studies-2 (QUADAS-2) risk of bias assessment tool (Whiting 2011).*

Study	Outcome	Risk of bias			Overall
		Patient selection	Index tests	Flow	
Hansen 2018	ISUP grade ≥2 prostate cancer	Low	Unclear	Low	Unclear
Mortezavi 2018	ISUP grade ≥2 prostate cancer	Low	Unclear	Low	Unclear
Bonekamp 2019	ISUP grade ≥2 prostate cancer	Low	Unclear	Low	Unclear
Bonekamp 2019	ISUP grade ≥3 prostate cancer	Low	Unclear	Low	Unclear

ISUP = International Society of Urological Pathology

3. GRADE certainty of evidence

Detection of clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) – Table 7

Detection of ISUP grade ≥ 3 prostate cancer – Table 8

Detection of ISUP grade 1 prostate cancer – no results

Table 7. *GRADE assessment of the certainty of the evidence for the sensitivity of MRI-targeted biopsy relative to combined systematic and MRI-targeted biopsy to detect ISUP Grade ≥ 2 prostate cancer in biopsy-naïve men with mpMRI score 4-5 lesion*

GRADE domain	*Rating*	*Reason for rating*	*Certainty of evidence*
Risk of bias	No serious concerns	All 3 studies reported this outcome and none of the sources of bias were considered to be at high risk of bias. The overall risk of bias was unclear due to unclear blinding of the index test, but this was not considered likely to have caused major distortions to the results for this PICO.	*HIGH*
Indirectness	No serious concerns	All 3 studies performed a systematic biopsy consisting of ≥20 cores for all men, which is the recommended standard of care in the Australian setting. Two of the three studies reported results for targeted biopsy alone whereas the third study reported results for biopsies within the MRI-positive area rather than targeted biopsies (Bonekamp 2019). Only one study used PIRADS v2 exclusively; one study used primarily PIRADS v1 and the other study used a Likert scale.	
Imprecision	No serious concerns with respect to whether the number of clinically significant cancers undetected were clinically important or unimportant	If prevalence of ISUP Grade ≥ 2 prostate cancer is 70%, in a population of 1000 biopsy-naïve men with mpMRI score 4-5 lesion, 252 (98, 434) ISUP Grade ≥ 2 prostate cancers would not be detected if perform MRI-targeted biopsy only. For ISUP Grade ≥ 2 prostate cancer not detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI crossed two thresholds, but it did not cross the threshold for a clinically **unimportant** difference. Sensitivity analysis excluding Bonekamp 2019 (study reporting the lowest relative sensitivity): If prevalence of ISUP Grade ≥ 2 prostate cancer is 70%, in a population of 1000 biopsy-naïve men with mpMRI score 4-5 lesion, 175 (63, 329) ISUP Grade ≥ 2 prostate cancers would not be detected if perform MRI-targeted biopsy only. For ISUP Grade ≥ 2 prostate cancer not detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI crossed two thresholds, but it did not cross the threshold for a clinically **unimportant** difference.	
Inconsistency	No serious concerns	There were > 10 percentage points between highest and lowest point estimates for relative sensitivity, and CIs did not overlap (Hansen 2018 0.83 (95% CI 0.79, 0.88), Bonekamp 2019 0.41 (95% CI 0.29, 0.52)). Significant heterogeneity was observed when results of the 3 studies were pooled (I^2 = 95.1%, p=0.00). The lower relative sensitivity reported by Bonekamp 2019 could be explained by results being reported for cancers detected in the MRI positive area, rather than for targeted biopsies, however such an approach would potentially result in larger estimates of the relative sensitivity for targeted biopsies. Differences in relative sensitivity may also be explained by differences in the MRI assessment tools used in each study i.e. PIRADS v2, PIRADS v1 and a Likert scale, the experience of radiologists reading the MRI images and the order in which biopsies were taken.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 studies. All 3 studies either reported no direct funding by industry and/or declared no conflicts of interest.	

CI = confidence interval; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging

Table 8. *GRADE assessment of the certainty of the evidence for the sensitivity of MRI-targeted biopsy relative to combined systematic and MRI-targeted biopsy to detect ISUP Grade ≥ 3 prostate cancer in biopsy-naïve men with mpMRI score 4-5 lesion*

GRADE domain	*Rating*	*Reason for rating*	*Certainty of evidence*
Risk of bias	No serious concerns	One study (Bonekamp 2019) assessed this outcome and none of the sources of bias were considered to be at high risk of bias. The overall risk of bias was unclear due to unclear blinding of the index test, but this was not considered likely to have caused major distortions to the results for this PICO.	*HIGH*
Indirectness	No serious concerns	The single study reporting this outcome performed a systematic biopsy consisting of ≥20 cores for all men, which is recommended as the standard of care in the Australian setting and used PIRADS v2 to assess MRIs. This study reported results for biopsies within the MRI-positive area rather than targeted biopsies (Bonekamp 2019).	
Imprecision	No serious concerns with respect to whether the number of clinically significant cancers undetected were clinically important or unimportant	If prevalence of ISUP Grade ≥ 3 prostate cancer is 30%, in a population of 1000 biopsy-naïve men with mpMRI score 4-5 lesion, 174 (120, 225) ISUP Grade ≥ 3 prostate cancers would not be detected if perform MRI-targeted biopsy only. For ISUP Grade ≥ 2 prostate cancer not detected using a MCID of 35/1000 and thresholds for moderate and large effects of 70/1000 and 140/1000 the 95%CI crossed one threshold, but it did not cross the threshold for a clinically **unimportant** difference.	
Inconsistency	Not assessable	Single study reporting this outcome.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 studies. The study reported no direct funding by industry and/or declared no conflicts of interest.	

CI = confidence interval; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging

4. Summary of findings

Table 9. *Summary of findings for MRI-targeted biopsy alone compared to combined systematic and MRI-targeted biopsy in biopsy-naïve men with mpMRI score 4-5 lesion*

Outcome ***(MCID)***	***Studies (participants)***	***Summary relative sensitivity***	***Outcome prevalence***	***Numbers undetected per 1000 if perform MRI-targeted biopsy only*** *(95% CI)*	***Certainty of the evidence (GRADE)***	***Plain text summary***
Clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) (50/1000)	3 (559)	0.64 (0.38, 0.86)	70%	252 (98, 434)	High	For biopsy-naïve men with a mpMRI score 4-5 lesion a **clinically important** (large or moderate)^ number of clinically significant cancers will not be detected if a ≥ 20 core systematic biopsy is not undertaken in addition to a targeted biopsy
	*Sensitivity analysis** 2 (448)	0.75 (0.53, 0.91)	70%	175 (63, 329)		
ISUP grade ≥ 3 prostate cancer (35/1000)	1 (111)	0.42 (0.25, 0.60)	30%	174 (120, 225)	High	For biopsy-naïve men with a mpMRI PIRADS 4-5 lesion a **clinically important** (large)^^ number of ISUP grade ≥ 3 cancers will not be detected if a ≥ 20 core systematic biopsy is not undertaken in addition to a targeted biopsy
ISUP grade 1 prostate cancer (100/1000)	0	No results found				No evidence found

CI = confidence interval; ISUP = International Society of Urological Pathology grade; MCID = minimal clinically important difference; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging

** Excluded study reporting the lowest relative sensitivity*

^ Using thresholds of 50/1000, 100/1000 and 200/1000 for small, moderate and large effects

^^ Using thresholds of 35/1000, 70/1000 and 140/1000 for small, moderate and large effects

5. Ongoing clinical trials

One potentially relevant ongoing trial protocol was identified by searches of clinical trial registries or literature searches.

Table 10. *Summary of potentially relevant ongoing randomised controlled trial comparing biopsy protocols with lower numbers of biopsy cores which include a targeted biopsy with a systematic biopsy of ≥ 20 cores with or without MRI-targeted biopsy*

Study ID Publications	Study name, location and study design	Start date	Planned completion date	Population	Intervention	Comparator	Outcomes
NCT04685928	Extended Systematic Versus Mri-Assisted pRostate Transperineal Biopsy (SMART) trial Hong Kong RCT – 2 arms	2021 Recruiting	2025	Biopsy-naïve men aged ≥18 years with clinical suspicion of prostate cancer based on elevated PSA (4-20 ng/ml) +/- abnormal DRE	mpMRI If PIRADS score 3-5, transperineal MRI-targeted biopsy (3-4 cores) + 12-core systematic biopsy (sparing MRI targets) If PIRADS score 1-2, no biopsy	No mpMRI Transperineal 24-core systematic biopsy for all men	*Primary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection *Secondary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection of MRI-targeted biopsy only vs systematic biopsy only Clinically insignificant prostate cancer (ISUP Grade 1) detection Biopsies avoided among mpMRI negative men Maximum cancer core length Adverse events at 30 days post biopsy Health-related quality of life Cost per diagnosis of cancer

DRE = digital rectal examination; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PIRADS = Prostate Image-Reporting and Data System; RCT = randomised controlled trial

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Hansen NL, Barrett T, Kesch C, et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer. BJU Int. 2018 Jul;122(1):40-49.

Mortezavi A, Märzendorfer O, Donati OF, et al. Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging and Fusion Guided Targeted Biopsy Evaluated by Transperineal Template Saturation Prostate Biopsy for the Detection and Characterization of Prostate Cancer. J Urol. 2018 Aug;200(2):309-318.

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APPENDICES

A.1 Search strategies for systematic reviews published 2010 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2010 -Current"
20	(Systematic* adj3 review*).tw.
21	(meta-analys* or meta analys*).tw.
22	20 or 21
23	19 and 22
24	remove duplicates from 23

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2010 and Jan 2025, in Cochrane Reviews (Word variations have been searched)

A.2a Search strategies for primary randomised controlled trials published 2018 onwards

Databases: Medline, Embase and Cochrane Central Register of Controlled Trials databases (via Ovid platform)

#	Searches
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
21	Randomized Controlled Trial/
22	exp Randomized Controlled Trials as Topic/
23	"Randomized Controlled Trial (topic)"/
24	Controlled Clinical Trial/
25	exp Controlled Clinical Trials as Topic/
26	"Controlled Clinical Trial (topic)"/
27	Randomization/
28	Random Allocation/
29	Double-Blind Method/
30	Double Blind Procedure/
31	Double-Blind Studies/
32	Single-Blind Method/
33	Single Blind Procedure/
34	Single-Blind Studies/
35	Placebos/
36	Placebo/
37	Control Groups/
38	Control Group/
39	(random* or sham or placebo*).ti,ab,hw,kf.
40	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
41	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
42	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
43	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
44	allocated.ti,ab,hw.
45	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
46	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
47	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
48	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
49	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
50	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
51	or/20-50
52	19 and 51
53	remove duplicates from 52

A.2b Search strategies for primary studies published 2018 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	from 19 keep 1-6000
21	remove duplicates from 20
22	from 19 keep 6001-7458
23	remove duplicates from 22
24	21 or 23
25	remove duplicates from 24

Appendix B: GRADE assessment of the certainty of the evidence

Ratings	*Definitions*
⨁⨁⨁⨁ High certainty	The panel is very confident that the true effect lies close to that of the estimate of the effect
⨁⨁⨁◯ Moderate certainty	The panel is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁◯◯ Low certainty	The panel's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁◯◯◯ Very low certainty	The panel has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reported based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Systematic reviews of the evidence were not accessible.

Appendix D: Excluded Studies

Article	*DOI*	*Reason for exclusion*
Articles from primary studies search for randomised controlled trials		
Ahlberg 2019	https://dx.doi.org/10.1136/bmjopen-2018-027860	Irrelevant population
Alberts 2019	https://dx.doi.org/10.1016/j.eururo.2018.07.031	Excluded study design
Alkema 2022	https://dx.doi.org/10.1016/j.euros.2022.08.005	Excluded study design
Alterbeck 2024	https://dx.doi.org/10.1111/bju.16143	Excluded study design
Amin 2020	https://dx.doi.org/10.1111/bju.14999	Excluded study design
Arsov 2022	https://dx.doi.org/10.1002/ijc.33940	Irrelevant population
Auvinen 2024	https://dx.doi.org/10.1001/jama.2024.3841	Irrelevant population
Baccaglini 2021	https://dx.doi.org/10.1016/j.clgc.2020.06.008	Excluded study design
Bates 2023	https://doi.org/10.1016/S0302-2838(23)00144-6	Excluded publication type
Bjornebo 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.7131	Irrelevant population
Boschheidgen 2024	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Excluded study design
Bratt 2019	https://dx.doi.org/10.1016/j.eururo.2019.02.035	Irrelevant population
Bryant 2023	https://dx.doi.org/10.1111/bju.15978	Irrelevant comparator
Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Excluded study design
Checcucci 2022	https://doi.org/10.1016/S2666-1683(22)01175-2	Excluded publication type
Checcucci 2023	https://doi.org/10.21873/anticanres.16021	Excluded publication type
Checcucci 2024	https://doi.org/10.1016/S0302-2838(22)00538-3	Excluded publication type
Checcucci 2022	https://doi.org/10.1097/JU.0000000000002555.11	Excluded publication type
Chen 2018	https://dx.doi.org/10.1016/j.ajur.2017.07.001	Excluded study design
ChiCTR2000036915 2020	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000036915	Excluded publication type
Choi 2019	https://dx.doi.org/10.1016/j.clgc.2018.09.007	Excluded study design
Dadpour 2023	https://pubmed.ncbi.nlm.nih.gov/37645612/	Irrelevant population
DRKS00032422 2023	https://drks.de/search/en/trial/DRKS00032422	Excluded publication type
Eineluoto 2018	https://dx.doi.org/10.1016/j.euo.2018.02.005	Excluded study design
Eklund 2021	https://dx.doi.org/10.1056/NEJMoa2100852	Irrelevant comparator
Elwenspoek 2019	https://dx.doi.org/10.1001/jamanetworkopen.2019.8427	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Excluded study design
Ettala 2022	https://dx.doi.org/10.1136/bmjopen-2021-053118	Irrelevant intervention
Exterkate 2020	https://dx.doi.org/10.1016/j.euo.2019.06.005	Irrelevant population
Exterkate 2023	https://dx.doi.org/10.1111/bju.15876	Irrelevant population
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	Irrelevant comparator
Ghai 2024	https://dx.doi.org/10.1148/radiol.231948	Irrelevant population
Guo 2024	https://dx.doi.org/10.1186/s13244-024-01699-4	Excluded study design
Hamid 2019	https://dx.doi.org/10.1016/j.eururo.2018.08.007	Excluded study design

He 2021	https://dx.doi.org/10.1136/bmjopen-2020-041427	Excluded publication type
Hu 2020	https://dx.doi.org/10.1007/s00261-019-02370-z	Irrelevant comparator
Hugosson 2022	https://dx.doi.org/10.1056/NEJMoa2209454	Irrelevant comparator
Hugosson 2019	https://doi.org/10.1016/S1569-9056(19)31108-X	Excluded publication type
Israel 2022	https://dx.doi.org/10.1111/bju.15562	Excluded study design
ISRCTN60263108 2022	https://www.isrctn.com/ISRCTN60263108	Excluded publication type
Izadpanahi 2021	https://dx.doi.org/10.1038/s41391-021-00366-9	Irrelevant comparator
Jahnen 2024	https://doi.org/10.1016/S0302-2838(24)00876-5	Excluded publication type
Jahnen 2023	https://doi.org/10.1016/S0302-2838(23)00355-X	Excluded publication type
Jiang 2024	https://dx.doi.org/10.1016/j.euo.2023.12.002	Irrelevant comparator
Kasivisvanathan 2018	https://dx.doi.org/10.1056/NEJMoa1801993	Irrelevant comparator
Kasivisvanathan 2019	https://dx.doi.org/10.1016/j.eururo.2019.04.043	Irrelevant comparator
Kasivisvanathan 2022	https://dx.doi.org/10.1371/journal.pone.0263345	Irrelevant comparator
Kelly 2023	https://dx.doi.org/10.1016/j.euros.2023.05.002	Excluded study design
Klotz 2020	https://dx.doi.org/10.1016/j.eururo.2019.10.007	Irrelevant population
Klotz 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7589	Irrelevant comparator
Klotz 2022	https://dx.doi.org/10.1016/j.cct.2021.106618	Irrelevant intervention
Klotz 2024	https://dx.doi.org/10.1016/j.euo.2023.09.013	Irrelevant population
Kohestani 2021	https://dx.doi.org/10.1080/21681805.2021.1881612	Irrelevant population
Kruger-Stokke 2021	https://dx.doi.org/10.3389/fonc.2021.745657	Irrelevant comparator
Liu 2024	https://dx.doi.org/10.1136/bmjopen-2023-080593	Excluded study design
Luzzago 2021	https://dx.doi.org/10.1038/s41391-020-00290-4	Excluded study design
Mian 2024	https://dx.doi.org/10.1097/JU.0000000000003979	Excluded study design
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	Excluded study design
Morote 2024	https://dx.doi.org/10.3390/cancers16132306	Excluded study design
NCT03572946 2018	https://clinicaltrials.gov/study/NCT03572946	Excluded publication type
NCT04993508 2021	https://clinicaltrials.gov/study/NCT04993508	Excluded publication type
NCT04953351 2021	https://clinicaltrials.gov/study/NCT04953351	Excluded publication type
NCT06303622 2024	https://clinicaltrials.gov/study/NCT06303622	Excluded publication type
NCT03632655 2018	https://clinicaltrials.gov/study/NCT03632655	Excluded publication type
NICE 2019	https://www.ncbi.nlm.nih.gov/books/NBK576979/	Excluded study design
Nordstrom 2021	https://dx.doi.org/10.1016/S1470-2045%2821%2900348-X	Irrelevant population
Nordstrom 2024	https://dx.doi.org/10.1001/jamanetworkopen.2023.54577	Irrelevant population
Panebianco 2018	https://dx.doi.org/10.1016/j.euo.2018.03.008	Irrelevant outcome
Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Porpiglia 2023	https://dx.doi.org/10.23736/S2724-6051.22.05189-8	Irrelevant comparator
Porreca 2020	https://dx.doi.org/10.1097/MD.0000000000022059	Irrelevant population
Prince 2021	https://dx.doi.org/10.2214/AJR.20.25207	Excluded study design
Rabah 2021	https://dx.doi.org/10.15537/smj.2021.42.6.20200771	Irrelevant comparator
Rai 2021	https://dx.doi.org/10.1016/j.euo.2020.12.012	Irrelevant comparator
Rakauskas 2023	https://dx.doi.org/10.1371/journal.pone.0280262	Excluded study design
Russo 2021	https://dx.doi.org/10.1016/j.euo.2021.03.007	Irrelevant comparator
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	Irrelevant population
Schiavina 2021	https://dx.doi.org/10.1016/j.urolonc.2020.10.018	Irrelevant population

Szewczyk-Bieda 2019	https://dx.doi.org/10.1186/s13063-019-3746-0	Irrelevant comparator
Wagensveld 2021	https://doi.org/10.1016/S0302-2838(21)01279-3	Excluded publication type
Wang 2023	https://dx.doi.org/10.1007/s00345-022-04086-0	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.eururo.2018.11.040	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.euo.2019.08.007	Irrelevant population
Wei 2023	https://dx.doi.org/10.1148/radiol.221428	Irrelevant population
Woo 2019	https://dx.doi.org/10.1016/j.euo.2019.05.004	Irrelevant comparator
Yang 2024	https://dx.doi.org/10.1016/j.acra.2024.08.027	Excluded study design
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Excluded study design
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant comparator
Zhang 2022	https://dx.doi.org/10.3389/fsurg.2022.1058288	Irrelevant comparator
Zhu 2018	https://dx.doi.org/10.7150/jca.24690	Irrelevant comparator
Articles from primary studies search and citation search for head-to-head studies		
Agrotis 2023	https://dx.doi.org/10.1002/jcu.23497	Irrelevant comparator
Ahdoot 2020	https://dx.doi.org/10.1056/NEJMoa1910038	Irrelevant comparator
Ahmed 2017	https://doi.org/10.1016/S0140-6736(16)32401-1	Irrelevant intervention
Alqahtani 2021	https://dx.doi.org/10.3390/cancers14010001	Irrelevant comparator
Alqahtani 2022	https://dx.doi.org/10.3390/cancers14010001	Irrelevant comparator
An 2024	https://dx.doi.org/10.1007/s00345-024-04947-w	Irrelevant comparator
Andras 2019	https://dx.doi.org/10.11152/mu-1705	Irrelevant comparator
Araujo 2023	https://dx.doi.org/10.4081/aiua.2023.11830	Irrelevant comparator
Avolio 2023	https://dx.doi.org/10.1007/s00345-023-04480-2	Irrelevant comparator
Bangash 2021	https://dx.doi.org/10.53350/pjmhs2115102625	Irrelevant population
Barrett 2019	https://dx.doi.org/10.1016/j.crad.2019.06.004	Irrelevant comparator
Barrett 2016	https://doi.org/10.1007/s00345-015-1650-0	Irrelevant population
Barth 2021	https://dx.doi.org/10.1016/j.ejro.2021.100332	Irrelevant intervention
Bass 2018	https://dx.doi.org/10.1136/bmjopen-2018-024941	Irrelevant comparator
Bastian-Jordan 2018	https://dx.doi.org/10.1111/1754-9485.12678	Irrelevant comparator
Bhat 2020	https://dx.doi.org/10.1080/13685538.2019.1641796	Irrelevant population
Boeve 2023	https://dx.doi.org/10.1111/bju.16041	No comparative data for outcome
Borghesi 2021	https://dx.doi.org/10.23736/S2724-6051.20.03758-3	Irrelevant comparator
Bosaily 2020	https://dx.doi.org/10.1016/j.eururo.2020.03.002	Irrelevant intervention
Boschheidgen 2023	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Irrelevant comparator
Bourgeno 2024	https://dx.doi.org/10.1016/j.euo.2024.01.007	Irrelevant comparator
Briggs 2021	https://dx.doi.org/10.1016/j.urology.2021.04.040	Irrelevant population
BrizmohunAppayya 2018	https://dx.doi.org/10.1259/bjr.20170645	Irrelevant population
Camacho 2023	https://doi.org/10.1002/bco2.231	Irrelevant comparator
Cetin 2023	https://dx.doi.org/10.18621/eurj.1198992	Irrelevant population
Chaloupka 2023	https://dx.doi.org/10.1111/bju.16248	Irrelevant comparator
Chandra Engel 2024	https://doi.org/10.1016/j.euo.2024.10.002	Irrelevant comparator
Chau 2018	https://dx.doi.org/10.1016/j.ijso.2018.01.002	Irrelevant population
Chau 2024	https://dx.doi.org/10.1007/s11845-024-03637-1	Irrelevant comparator
Checcucci 2020	https://dx.doi.org/10.23736/S0393-2249.20.03958-2	Irrelevant comparator

Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Irrelevant comparator
Cheng 2021	https://dx.doi.org/10.3389/fonc.2021.643051	Irrelevant comparator
Cheng 2022	https://dx.doi.org/10.1080/08941939.2020.1825884	Irrelevant comparator
Choomark 2023	https://dx.doi.org/10.33192/smj.v75i11.265361	Irrelevant comparator
Connor 2020	https://dx.doi.org/10.1097/JU.0000000000001184	Irrelevant comparator
D'Agostino 2019	https://dx.doi.org/10.4081/aiua.2019.2.87	Irrelevant comparator
D'Agostino 2020	https://dx.doi.org/10.4081/aiua.2019.4.211	Irrelevant comparator
Dahl 2022	https://dx.doi.org/10.1016/j.urolonc.2022.07.011	Irrelevant population
Dahl 2024	https://dx.doi.org/10.1016/j.urolonc.2023.11.004	Irrelevant population
Del Monte 2018	https://dx.doi.org/10.1007/s11547-017-0825-8	Irrelevant comparator
Dell'Oglio 2020	https://dx.doi.org/10.1016/j.euo.2019.03.002	Irrelevant comparator
Demirtas 2019	https://dx.doi.org/10.7759/cureus.6160	Irrelevant comparator
Deniffel 2022	https://dx.doi.org/10.1007/s00330-022-08822-3	Irrelevant population
Dhir 2023	https://dx.doi.org/10.1016/j.urology.2023.04.017	Irrelevant comparator
Diez 2024	https://doi.org/10.1007/s00345-024-05233-5	No comparative data for outcome
Donato 2020	https://dx.doi.org/10.1007/s00345-019-02774-y	Irrelevant comparator
Dragoescu 2023	https://dx.doi.org/10.3390/diagnostics13081373	Irrelevant comparator
Droghetti 2023	https://dx.doi.org/10.1007/s00345-022-04229-3	Irrelevant comparator
Eldred-Evans 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7456	Irrelevant comparator
Elfatairy 2019	https://dx.doi.org/10.1148/rycan.2019190016	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.2967/jnumed.121.263448	Excluded study design
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Irrelevant intervention
Emmett 2023	https://dx.doi.org/10.2967/jnumed.123.266164	Irrelevant intervention
Falagario 2021	https://dx.doi.org/10.1111/iju.14385	Irrelevant comparator
Fleville 2024	https://dx.doi.org/10.1097/JU.0000000000004226	Irrelevant comparator
Freifeld 2019	https://dx.doi.org/10.1016/j.urolonc.2018.10.009	Irrelevant comparator
Fulco 2021	https://dx.doi.org/10.3390/cancers13194833	Irrelevant comparator
Furrer 2022	https://dx.doi.org/10.1111/ans.17713	Irrelevant comparator
Gavin 2020	https://dx.doi.org/10.1016/j.euros.2020.07.001	Irrelevant population
Gayet 2020	https://dx.doi.org/10.1155/2020/4626781	Irrelevant comparator
Gomez-Gomez 2021	https://dx.doi.org/10.3390/diagnostics11081335	Irrelevant comparator
Gorin 2020	https://dx.doi.org/10.1007/s00345-019-02992-4	Irrelevant comparator
Gortz 2022	https://dx.doi.org/10.3390/cancers14040886	Irrelevant population
Grey 2022	https://dx.doi.org/10.1016/S1470-2045(22)00016-X	Irrelevant comparator
Gross 2020	https://dx.doi.org/10.1097/JU.0000000000000534	Irrelevant comparator
Gunzel 2022	https://dx.doi.org/10.1007/s11255-022-03309-y	Irrelevant comparator
Hagens 2022	https://dx.doi.org/10.1016/j.euros.2022.07.006	Irrelevant comparator
Hagens 2022	https://dx.doi.org/10.1016/j.euros.2022.04.001	Irrelevant population
Hansen 2020	https://dx.doi.org/10.1111/bju.14865	Irrelevant population
Henning 2021	https://dx.doi.org/10.1016/j.urolonc.2020.11.018	Irrelevant comparator
Hepp 2022	https://dx.doi.org/10.1007/s00345-022-03991-8	Irrelevant population
Ho 2023	https://dx.doi.org/10.1016/j.urolonc.2023.11.005	Irrelevant population
Hofbauer 2022	https://dx.doi.org/10.1111/bju.15635	Irrelevant population

Hogan 2022	https://dx.doi.org/10.1177/20514158221084820	No comparative data for outcome
Hogan 2024	https://dx.doi.org/10.1177/20514158221084820	Duplicate
Hou 2022	https://dx.doi.org/10.1038/s41391-021-00489-z	Irrelevant comparator
Hsi 2023	https://dx.doi.org/10.1002/bco2.184	No comparative data for outcome
Hsieh 2022	https://dx.doi.org/10.31083/j.jomh1806127	Irrelevant population
Huang 2022	https://dx.doi.org/10.2147/CMAR.S350701	Irrelevant comparator
Hubbard 2021	https://pubmed.ncbi.nlm.nih.gov/34786148/	Irrelevant population
Hung 2024	https://dx.doi.org/10.1016/j.urology.2023.11.039	Irrelevant comparator
Jahnen 2023	https://dx.doi.org/10.1007/s00345-023-04564-z	Irrelevant comparator
Kachanov 2022	https://dx.doi.org/10.1097/JU.0000000000002248	Irrelevant comparator
Kalapara 2022	https://dx.doi.org/10.1016/j.euo.2021.02.006	No comparative data for outcome
Kam 2018	https://dx.doi.org/10.1016/j.prnil.2017.10.003	Irrelevant population
Kasivisvanathan 2024	https://doi.org/10.1016/j.eururo.2024.08.022	Irrelevant comparator
Kato 2021	https://dx.doi.org/10.3390/curroncol28020123	Irrelevant comparator
Kaufmann 2022	https://dx.doi.org/10.1002/pros.24286	Irrelevant population
Khoo 2021	https://dx.doi.org/10.1097/JU.0000000000001476	Irrelevant population
Kim 2021	https://dx.doi.org/10.1007/s00330-020-07167-z	Irrelevant comparator
Kim 2022	https://dx.doi.org/10.1097/JU.0000000000002168	No comparative data for outcome
Kong 2023	https://dx.doi.org/10.1177/20514158211065946	No comparative data for outcome
Kortenbach 2021	https://dx.doi.org/10.1016/j.heliyon.2021.e08325	No comparative data for outcome
Krausewitz 2023	https://dx.doi.org/10.1007/s00345-022-04230-w	Irrelevant comparator
Kuhlmann 2022	https://dx.doi.org/10.1016/j.urolonc.2021.12.016	Irrelevant comparator
Kurokawa 2024	https://dx.doi.org/10.21873/anticanres.16858	Irrelevant comparator
Kwon 2023	https://dx.doi.org/10.1007/s11255-023-03674-2	No comparative data for outcome
Labra 2020	https://dx.doi.org/10.1007/s00261-020-02481-y	Irrelevant comparator
Lahoud 2021	https://dx.doi.org/10.1111/ans.16524	No comparative data for outcome
Lee 2020	https://dx.doi.org/10.1111/bju.15118	No comparative data for outcome
Lee 2021	https://dx.doi.org/10.1016/j.urolonc.2021.02.027	Overlapping data
Lee 2022	https://dx.doi.org/10.1016/j.prnil.2021.08.003	Irrelevant population
Lee 2022	https://dx.doi.org/10.1038/s41391-021-00485-3	Irrelevant comparator
Leow 2023	https://dx.doi.org/10.4103/aja2021128	Irrelevant comparator
Liu 2020	https://dx.doi.org/10.1038/s41391-020-0260-0	Irrelevant comparator
Liu 2021	https://dx.doi.org/10.1259/bjr.20210312	Irrelevant comparator
Liu 2023	https://dx.doi.org/10.1002/jmri.28614	Irrelevant comparator
Lockhart 2022	https://dx.doi.org/10.1177/20514158221085081	No comparative data for outcome
Lombardo 2023	https://dx.doi.org/10.3390/life13081719	Irrelevant comparator
Lopez 2021	https://dx.doi.org/10.1111/bju.15337	No comparative data for outcome
Lovegrove 2020	https://dx.doi.org/10.1097/JU.0000000000000455	Irrelevant intervention
Lughezzani 2019	https://dx.doi.org/10.1016/j.euo.2018.10.001	Irrelevant comparator

Malewski 2023	https://dx.doi.org/10.3390/jcm12175612	Irrelevant comparator
Martin 2023	https://dx.doi.org/10.1007/s00345-023-04386-z	Irrelevant comparator
Mesko 2018	https://dx.doi.org/10.1097/COC.0000000000000308	Irrelevant comparator
Miah 2020	https://dx.doi.org/10.1007/s11701-019-00929-y	Irrelevant population
Mischinger 2018	https://dx.doi.org/10.1111/bju.14089	Irrelevant comparator
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	No comparative data for outcome
Morote 2023	https://dx.doi.org/10.3390/cancers15184543	Irrelevant comparator
Neale 2020	https://dx.doi.org/10.1111/bju.15092	Irrelevant population
Noujeim 2023	https://dx.doi.org/10.1038/s41391-022-00620-8	Irrelevant comparator
Novara 2023	https://dx.doi.org/10.1007/s00345-023-04382-3	Irrelevant outcome
Oderda 2024	https://dx.doi.org/10.3390/curroncol31070308	Irrelevant comparator
Oh 2020	https://dx.doi.org/10.4111/icu.2020.61.1.28	Irrelevant intervention
Olivetta 2024	https://dx.doi.org/10.3390/diagnostics14151643	Irrelevant comparator
Osses 2018	https://dx.doi.org/10.1159/000447216	Irrelevant comparator
Pang 2021	https://dx.doi.org/10.12998/wjcc.v9.i36.11183	Irrelevant comparator
Park 2020	https://dx.doi.org/10.3390/jcm9020530	Irrelevant comparator
Patel 2018	https://dx.doi.org/10.1016/j.euo.2018.03.009	Irrelevant comparator
Patel 2022	https://dx.doi.org/10.1097/JU.0000000000002120	Irrelevant comparator
Pepe 2022	https://dx.doi.org/10.21873/anticanres.15785	Irrelevant comparator
Petov 2023	https://dx.doi.org/10.1089/end.2022.0780	Irrelevant comparator
Phelps 2023	https://dx.doi.org/10.1007/s00261-022-03775-z	Irrelevant comparator
Ploussard 2019	https://dx.doi.org/10.1007/s00345-018-2399-z	Excluded study design
Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Pratihar 2023	https://dx.doi.org/10.4103/iju.iju_147_23	Irrelevant comparator
Rachubinski 2022	https://dx.doi.org/10.1097/JU.0000000000002921	Irrelevant population
Radtke 2019	https://dx.doi.org/10.1371/journal.pone.0221350	No comparative data for outcome
Rajendran 2024	https://dx.doi.org/10.1093/bjr/tqad027	No comparative data for outcome
Ruan 2023	https://dx.doi.org/10.1007/s00261-023-03894-1	Irrelevant comparator
Saba 2020	https://dx.doi.org/10.1097/JU.0000000000000622	No comparative data for outcome
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	No comparative data for outcome
Sanguedolce 2024	https://doi.org/10.1016/j.euo.2024.10.006	Irrelevant population
Sathianathen 2018	https://dx.doi.org/10.1038/s41391-018-0065-6	Irrelevant comparator
Sathianathen 2019	https://dx.doi.org/10.1111/bju.14617	Irrelevant comparator
Schelb 2019	https://dx.doi.org/10.1148/radiol.2019190938	Irrelevant outcome
Schmid 2023	https://dx.doi.org/10.1002/pros.24435	No comparative data for outcome
Senoglu 2022	https://dx.doi.org/10.4274/uob.galenos.2021.2021.4.1	Irrelevant comparator
Seref 2022	https://dx.doi.org/10.1002/pros.24255	Irrelevant population
Shefler 2024	https://dx.doi.org/10.1016/j.urolonc.2024.01.026	Irrelevant comparator
Siddiqui 2023	https://dx.doi.org/10.1038/s41391-023-00660-8	Irrelevant outcome
Sigle 2021	https://dx.doi.org/10.3390/cancers13102502	Irrelevant population
Sigle 2022	https://dx.doi.org/10.3390/cancers14215230	Irrelevant population

Sigle 2023	https://dx.doi.org/10.1016/j.euf.2023.01.020	Irrelevant population
Sivaraman 2022	https://dx.doi.org/10.4103/iju.iju_222_21	No comparative data for outcome
Song 2020	https://dx.doi.org/10.1097/JU.0000000000001302	Irrelevant comparator
Stabile 2021	https://dx.doi.org/10.1038/s41391-021-00371-y	Irrelevant comparator
Stavrinides 2023	https://dx.doi.org/10.1148/radiol.220762	Irrelevant population
Stevens 2023	https://dx.doi.org/10.1177/02841851231187135	Irrelevant intervention
Stone 2021	https://dx.doi.org/10.1002/bco2.111	Irrelevant intervention
Sugano 2020	https://dx.doi.org/10.1007/s11255-019-02354-4	Irrelevant comparator
Tae 2018	https://dx.doi.org/10.4111/icu.2018.59.6.363	Irrelevant comparator
Tay 2021	https://dx.doi.org/10.1002/bco2.99	Irrelevant intervention
Thangarasu 2021	https://dx.doi.org/10.2147/RRU.S300868	Irrelevant comparator
Thompson 2023	https://dx.doi.org/10.5152/tud.2023.22221	Irrelevant population
Tomioka 2023	https://dx.doi.org/10.3390/diagnostics13152608	Irrelevant comparator
Tschirdewahn 2021	https://dx.doi.org/10.1016/j.euf.2020.06.020	No comparative data for outcome
Tunc 2023	https://dx.doi.org/10.22037/uj.v20i.7610	Irrelevant comparator
Turkay 2020	https://dx.doi.org/10.1097/RUQ.0000000000000505	Irrelevant comparator
Velarde 2022	https://dx.doi.org/10.1007/s00261-021-03389-x	Irrelevant comparator
Wagaskar 2022	https://dx.doi.org/10.22037/uj.v18i.6852	No comparative data for outcome
Wang 2020	https://dx.doi.org/10.4103/aja.aja_83_19	Irrelevant comparator
Wang 2021	https://dx.doi.org/10.1186/s12894-021-00949-7	Irrelevant comparator
Washino 2018	https://dx.doi.org/10.1186/s12894-018-0361-4	Irrelevant comparator
Wei 2022	https://dx.doi.org/10.1007/s00261-022-03592-4	Irrelevant comparator
Weiser 2023	https://dx.doi.org/10.1002/jmri.28891	No comparative data for outcome
Wenzel 2021	https://dx.doi.org/10.3389/fsurg.2021.633196	Irrelevant intervention
Wong 2024	https://dx.doi.org/10.1016/j.euo.2024.01.002	No comparative data for outcome
Woo 2023	https://dx.doi.org/10.1016/j.euros.2022.11.012	Irrelevant comparator
Wu 2024	https://dx.doi.org/10.1038/s41391-023-00729-4	Irrelevant intervention
Yilmaz 2023	https://dx.doi.org/10.1148/radiol.221309	Irrelevant comparator
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Irrelevant population
Zambon 2024	https://dx.doi.org/10.1038/s41391-023-00770-3	Irrelevant comparator
Zattoni 2023	https://dx.doi.org/10.1007/s00345-023-04578-7	Irrelevant population
Zawaideh 2020	https://dx.doi.org/10.1259/bjr.20200298	Irrelevant comparator
Zhang 2018	https://dx.doi.org/10.1186/s12957-018-1367-9	Irrelevant intervention
Zhang 2019	https://dx.doi.org/10.1016/j.prnil.2018.10.001	Irrelevant comparator
Zhang 2020	https://dx.doi.org/10.1007/s10147-019-01524-9	Irrelevant population
Zhang 2020	https://dx.doi.org/10.21037/tau.2020.02.20	Irrelevant comparator
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant comparator
Zhang 2022	https://dx.doi.org/10.1186/s40644-022-00498-8	Irrelevant comparator
Zhu 2018	https://dx.doi.org/10.1097/MD.0000000000011962	Irrelevant comparator
Articles from Haider 2021 and Drost 2019 systematic reviews		
Alberts 2017	https://doi.org/10.1016/j.eururo.2017.06.019	Irrelevant comparator
Baco 2016	https://doi.org/10.1016/j.eururo.2015.03.041	Irrelevant comparator

Boesen 2018	https://doi.org/10.1001/jamanetworkopen.2018.0219	Irrelevant comparator
Borkowetz 2017	https://doi.org/10.1159/000477263	Irrelevant comparator
Borkowetz 2018	https://doi.org/10.1111/bju.14017	Irrelevant comparator
Castellucci 2017	https://doi.org/10.23736/s0393-2249.17.02845-4	Irrelevant comparator
Chen 2015	https://doi.org/10.3892%2Fetm.2014.2061	Irrelevant comparator
Cool 2016	https://doi.org/10.5489%2Fcuaj.3831	Irrelevant comparator
Delongchamps 2013	https://doi.org/10.1016/j.juro.2012.08.195	Irrelevant comparator
Distler 2017	https://doi.org/10.1016/j.juro.2017.03.130	Irrelevant population
Filson 2016	https://doi.org/10.1002/cncr.29874	Irrelevant comparator
Garcia Bennett 2017	https://doi.org/10.1016/j.diii.2017.06.010	Irrelevant comparator
Grey 2015	https://doi.org/10.1111/bju.12862	Irrelevant population
Gronberg 2018	https://doi.org/10.1016/j.eururo.2018.06.022	Irrelevant comparator
Jambor 2015	https://doi.org/10.1002/jmri.24682	Irrelevant comparator
Jambor 2017	https://doi.org/10.1002/jmri.25641	Irrelevant comparator
Kesch 2017	https://doi.org/10.1159/000458764	No comparative data for outcome
Kim 2017	https://doi.org/10.1016/j.urology.2016.08.074	Irrelevant comparator
Lee 2016	https://doi.org/10.3349/ymj.2016.57.3.565	Irrelevant comparator
Lee 2017	https://doi.org/10.3349%2Fymj.2017.58.5.994	Irrelevant comparator
Muthuveloe 2016	https://doi.org/10.5173/ceju.2016.675	Irrelevant population
Nafie 2014	https://pubmed.ncbi.nlm.nih.gov/28299763/	Irrelevant population
Okcelik 2016	https://doi.org/10.1590/s1677-5538.ibju.2015.0155	Irrelevant comparator
Panebianco 2015	https://doi.org/10.1016/j.urolonc.2014.09.013	Irrelevant comparator
Peltier 2015	https://doi.org/10.1155/2015/571708	Irrelevant comparator
Ploussard 2014	https://doi.org/10.1016/j.eururo.2012.05.049	Irrelevant population
Pokorny 2014	https://doi.org/10.1016/j.eururo.2014.03.002	Irrelevant comparator
Pressier 2019	https://doi.org/10.1016/j.euf.2019.06.015	Irrelevant comparator
Rouvière 2019	https://doi.org/10.1016/s1470-2045(18)30569-2	Irrelevant comparator
Sakar 2019	https://doi.org/10.1177/2051415819889552	Irrelevant comparator
Thompson 2016	https://doi.org/10.1016/j.juro.2015.10.140	No comparative data for outcome
Tonttilla 2016	https://doi.org/10.1016/j.eururo.2015.05.024	Irrelevant comparator
Van der Leest 2019	https://doi.org/10.1016/j.eururo.2018.11.023	Irrelevant comparator
Westoff 2019	https://doi.org/10.1016/j.urolonc.2019.07.004	Irrelevant comparator
Zalesky 2019	https://doi.org/10.5507/bp.2019.050	Irrelevant comparator
Zhang 2017	https://doi.org/10.1007/s11255-016-1484-8	Irrelevant comparator

3.11 Clinical question 8 – Prostate Biopsy PICO 8B

Clinical question: *For biopsy naïve men with a PI-RADS 4 or 5 lesion on multiparametric MRI (mpMRI) are targeted biopsies alone acceptable/ reasonable/ adequate? (is a systematic biopsy necessary?)*

Introduction

This is the second of three systematic reviews which address Clinical question 8.

Systematic review report for PICO 8B: Comparison of prostate cancer detection by mpMRI targeted biopsy plus 12-core vs ≥ 20-core systematic biopsy

Authors

Chelsea Carle, Suzanne Hughes

PICO

This systematic review addresses the following PICO which is summarised in detail in Table 1.

PICO 8B: *For biopsy naïve men with a PI-RADS 4 or 5 lesion on mpMRI how do the rates of clinically significant and insignificant cancers detected using a targeted biopsy together with a 12-core systematic biopsy compare with those using a targeted biopsy together with a 20 or more-core systematic biopsy?*

Table 1. *PICO components*

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Biopsy naïve individuals with a PI-RADS 4 or 5 lesion on mpMRI	MRI-targeted biopsy + 12-core systematic biopsy	MRI-targeted biopsy + ≥ 20 core systematic biopsy	Detection of • ≥ ISUP grade 2 prostate cancer • ISUP grade 1 prostate cancer • ≥ ISUP grade 3 prostate cancer	Randomized controlled trial Or Fully paired comparison

ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PI-RADS = Prostate Image-Reporting and Data System

1. Methods

1.1 Selection criteria

Table 2. *Selection criteria*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention or diagnostic accuracy	
Study design	Cross-sectional head-to-head (fully paired) studies, or Randomised controlled trials or Systematic reviews thereof	
Population	Biopsy naïve individuals with a PI-RADS or Likert score 4 or 5 lesion on mpMRI	> 10% of population have undergone prior biopsy and outcomes not stratified for biopsy-naïve patients. Prostate cancer patients (restricted to radical prostatectomy specimens) Not 5-point Likert scale.
Intervention	**MRI-targeted biopsy** • minimum 2-cores, • any fusion method (software registration, cognitive, in-bore) + **12-core** or < 20-core **systematic biopsy**	Single core targeted biopsy Perilesional biopsies
Comparator	≥ 20-core systematic biopsy • includes template biopsies, • transperineal or transrectal approach **+** MRI-targeted biopsy	Systematic or template biopsy < 20 cores. Systematic biopsy excludes regions sampled by targeted biopsy Biopsy approach differed from that used for the intervention
Outcome	Detection of: **ISUP grade ≥ 2 prostate cancer (primary outcome)**, or ISUP grade ≥ 3 prostate cancer, or ISUP grade 1 prostate cancer	ISUP grade ≥ 2 combined with a subgroup of ISUP grade 1 for example • Max CCL ≥5 mm for Gleason score 6 disease
Analyses	Per-patient	Per-lesion
Publication date	From 2010 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

CCL = cancer core length; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PI-RADS = Prostate Image-Reporting and Data System

1.2 Definitions and terminology

For the purposes of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).

ISUP grade ≥ 3 prostate cancer is prostate cancer scored as Gleason Score 7(4+3) or higher on histopathological findings (Epstein 2016).

ISUP grade 1 prostate cancer is prostate cancer scored as Gleason Score 6(3+3) on histopathological findings (Epstein 2016).

Multi-parametric MRI (mpMRI) refers to an imaging protocol used to detect and characterise tissue abnormalities to determine the presence and severity of cancer. Prostate mpMRI acquisition includes T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging.
Systematic biopsy refers to a biopsy in which cores are taken from areas of the prostate according to a template or pattern and includes saturation biopsies.
Targeted biopsy refers to a biopsy in which cores are taken from lesions identified on MRI as suspicious of harbouring significant cancer. Cognitive, software registration or in-bore image fusion techniques are used to identify lesions for biopsy.

- Cognitive image fusion refers to the operator visually fusing MRI images and real time ultrasound pictures.
- Software registration image fusion refers to using software to fuse uploaded MRI images to real time ultrasound.
- In-bore image fusion refers to fusing prior MRI images and a real time MRI during biopsy.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website

- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and as the evidence for mpMRI-targeted biopsy continues to evolve, be based on literature published up until 2022 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

A search for systematic reviews of prostate mpMRI published from 2010 onwards in Medline, Embase and Cochrane Systematic Review databases (search strategies in Appendix A) yielded 302 records. Two relevant systematic reviews were identified:

- Haider et al (2021), a systematic review for the Cancer Care Ontario Guideline 27-2 Version 2: *Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer,* captured relevant literature published from 1st May 2013 to 1st September 2020
- Drost et al (2019) captured relevant literature published from 1st January 1990 to 31st July 2018

We assessed studies included in the Haider 2021 and Drost 2019 systematic reviews for inclusion in our systematic review, and designed searches to identify randomised controlled trials and head-to-head (paired) studies or systematic reviews thereof published from 2018 onwards. Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations), Embase and Cochrane CENTRAL databases were searched initially on 6th December 2023 combining text terms and database-specific subject headings for

prostate cancer, multiparametric MRI and biopsy, and a filter for randomised controlled trials (RCT / CCT - MEDLINE, Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 2024-07-30.). Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st November 2024. The searches were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the searches is included as Appendix A. Reference lists of recent relevant guidelines and systematic reviews were checked for potential additional articles. If no relevant studies were found, in the case an article reported near-complete data to meet criteria for inclusion we contacted authors once via email to request additional data, e.g., if PIRADS-stratified outcome data were not available for a reported biopsy-naïve subgroup.

1.5 Data extraction and analyses

Extraction of the following study characteristics was planned: Country and year of publication, study setting and period, participant eligibility and age, details of mpMRI, MRI-targeted biopsy and systematic biopsy, and relevant comparisons and outcomes reported. We planned to calculate clinically significant prostate cancer undetected, and the relative sensitivity of the different biopsy approaches and to undertake pooled analyses if there were two or more studies reporting the same outcome.

1.6 Risk of bias assessments

Independent assessments of the risk of bias by two reviewers using Cochrane Collaboration Risk of Bias-II tool (Sterne 2019) for randomised controlled trials and using a modified version of the Quality of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool (Whiting 2011) were planned.

1.7 GRADE assessment of the certainty of the evidence

GRADE assessments were planned to assess the certainty of the body of evidence for each outcome. (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence). The certainty of the body of evidence would be rated *high*, *moderate*, *low* or *very low* based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Grade Handbook 2013), Schunemann 2020a, Schunemann 2020b and Schunemann 2022. As per GRADE guidance, studies started with a high level of certainty in the evidence and were to be downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

1.8 Clinical trial registry searches

Potentially relevant ongoing and unpublished trials were identified from literature and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 29 October 2024. The clinical trial registries were searched with the search terms listed below:

Clinicaltrials.gov using the terms:

“prostate cancer” and “multiparametric MRI” and “biopsy”

“prostate cancer” and “MRI” and “biopsy”

"prostate cancer" and "magnetic resonance imaging" and "biopsy"

International Clinical Trials Registry Platform using the terms:
"prostate cancer" and "multiparametric MRI" and "biopsy"
"prostate cancer" and "MRI" and "biopsy"
"prostate cancer" and "magnetic resonance imaging" and "biopsy"

Australia and New Zealand Clinical Trial Registry using the terms:
"prostate cancer" and "magnetic resonance imaging"
"prostate cancer" and "multiparametric MRI"
"prostate cancer" and "MRI"
"prostate cancer" and "biopsy"

2. Results

2.1 Guidelines searches

One potentially relevant guideline was identified which was based on systematic reviews of the literature published up until 2022 or later. It was not considered for adoption as the systematic reviews were not accessible (Appendix B).

2.2 Literature searches

The systematic search for studies published from 2018 onwards identified 5908 unique records to November 1st, 2024 (Figure 1). Of these, 284 full text articles were retrieved for a more detailed evaluation. 36 studies published to 2020 included in the Haider 2021 and Drost 2019 systematic reviews, and one article identified in a reference list were also assessed for inclusion. We found no randomised control trials or head-to-head (paired) studies that reported detection of clinically significant prostate cancer defined as ISUP grade ≥ 2 for the population and comparisons of interest. We contacted authors of two studies reporting near-complete data for additional information. Petov 2023 provided additional data, however the study was excluded as comparator data (combined systematic and MRI-targeted biopsy) results were unable to be extracted. Novara 2023 reported data for the population and comparisons of interest, however clinically significant prostate cancer was defined as Gleason score ≥ 4+3 (ISUP grade ≥3) and/or maximum core involvement 6 mm. The authors did not respond to our request for ISUP grade ≥ 2 data, and therefore the study was excluded.
There were no studies that included Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.
The retrieved articles that were not included in this systematic review and the reasons for their exclusion are documented in Appendix C. The main reasons for exclusion were irrelevant comparator or irrelevant population.

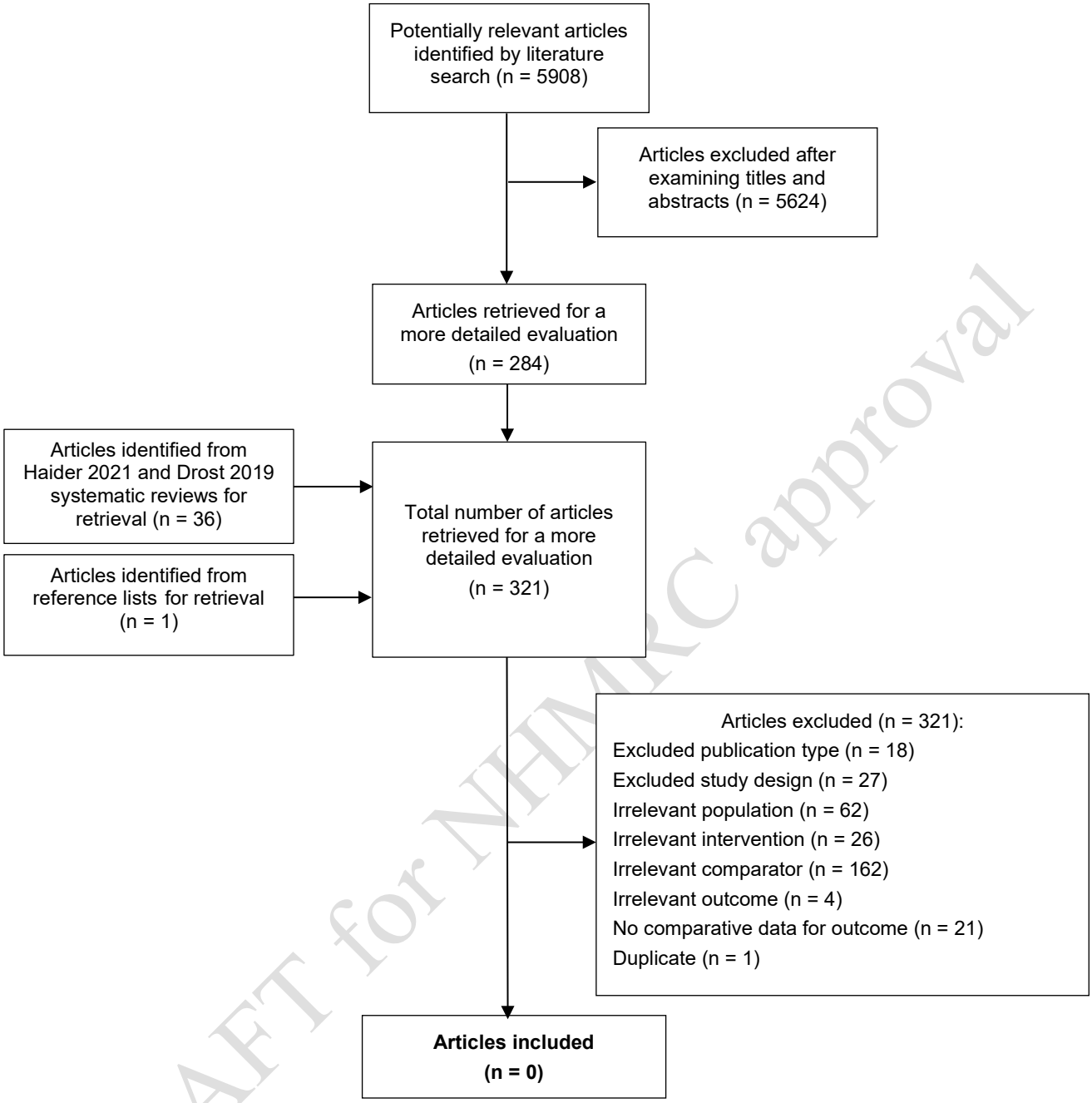

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

3. Ongoing clinical trials

One potentially relevant ongoing trial protocol was identified by searches of clinical trial registries or literature searches.

Table 3. *Summary of potentially relevant ongoing randomised controlled trial comparing biopsy protocols with lower numbers of biopsy cores which include a targeted biopsy with a systematic biopsy of ≥ 20 cores with or without MRI-targeted biopsy*

Study ID Publications	***Study name, location and study design***	***Start date***	***Planned completion date***	***Population***	***Intervention***	***Comparator***	***Outcomes***
NCT04685928	Extended Systematic Versus Mri-Assisted pRostate Transperineal Biopsy (SMART) trial Hong Kong RCT – 2 arms	2021 Recruiting	2025	Biopsy-naïve men aged ≥18 years with clinical suspicion of prostate cancer based on elevated PSA (4-20 ng/ml) +/- abnormal DRE	mpMRI If PIRADS score 3-5, transperineal MRI-targeted biopsy (3-4 cores) + 12-core systematic biopsy (sparing MRI targets) If PIRADS score 1-2, no biopsy	No mpMRI Transperineal 24-core systematic biopsy for all men	*Primary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection *Secondary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection of MRI-targeted biopsy only vs systematic biopsy only Clinically insignificant prostate cancer (ISUP Grade 1) detection Biopsies avoided among mpMRI negative men Maximum cancer core length Adverse events at 30 days post biopsy Health-related quality of life Cost per diagnosis of cancer

DRE = digital rectal examination; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PIRADS = Prostate Image-Reporting and Data System; RCT = randomised controlled trial

REFERENCES:

Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019 Apr 25;4(4):CD012663.

Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol. 2016 Feb;40(2):244-52.

Haider, M.A. et al. Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer: an Updated Systematic Review. Clinical Oncology. 2021 Dec; 33(12):e599 - e612.

Novara G, Zattoni F, Zecchini G, et al. Role of targeted biopsy, perilesional biopsy, and random biopsy in prostate cancer diagnosis by mpMRI/transrectal ultrasonography fusion biopsy. World J Urol. 2023;41(11):3239-3247.

Petov V, Bazarkin A, Morozov A, et al. A Prospective Comparison of Transrectal Standard, Cognitive, Transperineal Fusion, and Mapping Prostate Biopsy for Cancer Detection. J Endourol. 2023;37(8):940-947.

Schunemann H, Brozek J, Guyatt G, Oxman A, eds. Handbook for grading the quality of evidence and the strength of recommendation using the GRADE approach. Updated October 2013.

Schunemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 1. Study design, risk of bias and indirectness in rating the certainty of evidence across a body of evidence for test accuracy. J. Clin. Epidemiol. 2020a;122:129-141

Schunemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 2. Test accuracy: inconsistency, imprecision, publication bias, and other domains for rating the certainty of evidence and present it in evidence profiles and summary of findings tables. J. Clin. Epidemiol. 2020b;122:142-152.

Schunemann HJ, Neumann I, Hultcrantz M et al. 2022. GRADE guidance 35: Update on rating imprecision for assessing contextualized certainty of evidence and making decisions. J. Clin. Epidemiol. 150:225-242.

Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

Whiting PF, Rutjes AW, Westwood ME, QUADAS-2 Group, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36.

APPENDICES

A.1 Search strategies for systematic reviews published 2010 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2010 -Current"
20	(Systematic* adj3 review*).tw.
21	(meta-analys* or meta analys*).tw.
22	20 or 21
23	19 and 22
24	remove duplicates from 23

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2010 and Jan 2025, in Cochrane Reviews (Word variations have been searched)

A.2a Search strategies for primary randomised controlled trials published 2018 onwards

Databases: Medline, Embase and Cochrane Central Register of Controlled Trials databases (via Ovid platform)

#	Searches
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
21	Randomized Controlled Trial/
22	exp Randomized Controlled Trials as Topic/
23	"Randomized Controlled Trial (topic)"/
24	Controlled Clinical Trial/
25	exp Controlled Clinical Trials as Topic/
26	"Controlled Clinical Trial (topic)"/
27	Randomization/
28	Random Allocation/
29	Double-Blind Method/
30	Double Blind Procedure/
31	Double-Blind Studies/
32	Single-Blind Method/
33	Single Blind Procedure/
34	Single-Blind Studies/
35	Placebos/
36	Placebo/
37	Control Groups/
38	Control Group/
39	(random* or sham or placebo*).ti,ab,hw,kf.
40	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
41	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
42	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
43	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
44	allocated.ti,ab,hw.
45	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
46	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
47	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
48	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
49	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
50	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
51	or/20-50
52	19 and 51
53	remove duplicates from 52

A.2b Search strategies for primary studies published 2018 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	from 19 keep 1-6000
21	remove duplicates from 20
22	from 19 keep 6001-7458
23	remove duplicates from 22
24	21 or 23
25	remove duplicates from 24

Appendix B: Potentially relevant prostate cancer early detection and management guidelines reportedly based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Systematic reviews of the evidence were not accessible.

Appendix C: Excluded Studies

Article	*DOI*	*Reason for exclusion*
Articles from primary studies search for randomised controlled trials		
Ahlberg 2019	https://dx.doi.org/10.1136/bmjopen-2018-027860	Irrelevant population
Alberts 2019	https://dx.doi.org/10.1016/j.eururo.2018.07.031	Excluded study design
Alkema 2022	https://dx.doi.org/10.1016/j.euros.2022.08.005	Excluded study design
Alterbeck 2024	https://dx.doi.org/10.1111/bju.16143	Excluded study design
Amin 2020	https://dx.doi.org/10.1111/bju.14999	Excluded study design

Arsov 2022	https://dx.doi.org/10.1002/ijc.33940	Irrelevant population
Auvinen 2024	https://dx.doi.org/10.1001/jama.2024.3841	Irrelevant population
Baccaglini 2021	https://dx.doi.org/10.1016/j.clgc.2020.06.008	Excluded study design
Bates 2023	https://doi.org/10.1016/S0302-2838(23)00144-6	Excluded publication type
Bjornebo 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.7131	Irrelevant population
Boschheidgen 2024	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Excluded study design
Bratt 2019	https://dx.doi.org/10.1016/j.eururo.2019.02.035	Irrelevant population
Bryant 2023	https://dx.doi.org/10.1111/bju.15978	Irrelevant comparator
Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Excluded study design
Checcucci 2022	https://doi.org/10.1016/S2666-1683(22)01175-2	Excluded publication type
Checcucci 2023	https://doi.org/10.21873/anticanres.16021	Excluded publication type
Checcucci 2024	https://doi.org/10.1016/S0302-2838(22)00538-3	Excluded publication type
Checcucci 2022	https://doi.org/10.1097/JU.0000000000002555.11	Excluded publication type
Chen 2018	https://dx.doi.org/10.1016/j.ajur.2017.07.001	Excluded study design
ChiCTR2000036915 2020	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000036915	Excluded publication type
Choi 2019	https://dx.doi.org/10.1016/j.clgc.2018.09.007	Excluded study design
Dadpour 2023	https://pubmed.ncbi.nlm.nih.gov/37645612/	Irrelevant population
DRKS00032422 2023	https://drks.de/search/en/trial/DRKS00032422	Excluded publication type
Eineluoto 2018	https://dx.doi.org/10.1016/j.euo.2018.02.005	Excluded study design
Eklund 2021	https://dx.doi.org/10.1056/NEJMoa2100852	Irrelevant comparator
Elwenspoek 2019	https://dx.doi.org/10.1001/jamanetworkopen.2019.8427	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Excluded study design
Ettala 2022	https://dx.doi.org/10.1136/bmjopen-2021-053118	Irrelevant intervention
Exterkate 2020	https://dx.doi.org/10.1016/j.euo.2019.06.005	Irrelevant population
Exterkate 2023	https://dx.doi.org/10.1111/bju.15876	Irrelevant population
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	Irrelevant comparator
Ghai 2024	https://dx.doi.org/10.1148/radiol.231948	Irrelevant population
Guo 2024	https://dx.doi.org/10.1186/s13244-024-01699-4	Excluded study design
Hamid 2019	https://dx.doi.org/10.1016/j.eururo.2018.08.007	Excluded study design
He 2021	https://dx.doi.org/10.1136/bmjopen-2020-041427	Excluded publication type
Hu 2020	https://dx.doi.org/10.1007/s00261-019-02370-z	Irrelevant comparator
Hugosson 2022	https://dx.doi.org/10.1056/NEJMoa2209454	Irrelevant comparator
Hugosson 2019	https://doi.org/10.1016/S1569-9056(19)31108-X	Excluded publication type
Israel 2022	https://dx.doi.org/10.1111/bju.15562	Excluded study design
ISRCTN60263108 2022	https://www.isrctn.com/ISRCTN60263108	Excluded publication type
Izadpanahi 2021	https://dx.doi.org/10.1038/s41391-021-00366-9	Irrelevant comparator
Jahnen 2024	https://doi.org/10.1016/S0302-2838(24)00876-5	Excluded publication type
Jahnen 2023	https://doi.org/10.1016/S0302-2838(23)00355-X	Excluded publication type
Jiang 2024	https://dx.doi.org/10.1016/j.euo.2023.12.002	Irrelevant comparator
Kasivisvanathan 2018	https://dx.doi.org/10.1056/NEJMoa1801993	Irrelevant comparator
Kasivisvanathan 2019	https://dx.doi.org/10.1016/j.eururo.2019.04.043	Irrelevant comparator
Kasivisvanathan 2022	https://dx.doi.org/10.1371/journal.pone.0263345	Irrelevant comparator
Kelly 2023	https://dx.doi.org/10.1016/j.euros.2023.05.002	Excluded study design
Klotz 2020	https://dx.doi.org/10.1016/j.eururo.2019.10.007	Irrelevant population

Klotz 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7589	Irrelevant comparator
Klotz 2022	https://dx.doi.org/10.1016/j.cct.2021.106618	Irrelevant intervention
Klotz 2024	https://dx.doi.org/10.1016/j.euo.2023.09.013	Irrelevant population
Kohestani 2021	https://dx.doi.org/10.1080/21681805.2021.1881612	Irrelevant population
Kruger-Stokke 2021	https://dx.doi.org/10.3389/fonc.2021.745657	Irrelevant comparator
Liu 2024	https://dx.doi.org/10.1136/bmjopen-2023-080593	Excluded study design
Luzzago 2021	https://dx.doi.org/10.1038/s41391-020-00290-4	Excluded study design
Mian 2024	https://dx.doi.org/10.1097/JU.0000000000003979	Excluded study design
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	Excluded study design
Morote 2024	https://dx.doi.org/10.3390/cancers16132306	Excluded study design
NCT03572946 2018	https://clinicaltrials.gov/study/NCT03572946	Excluded publication type
NCT04993508 2021	https://clinicaltrials.gov/study/NCT04993508	Excluded publication type
NCT04953351 2021	https://clinicaltrials.gov/study/NCT04953351	Excluded publication type
NCT06303622 2024	https://clinicaltrials.gov/study/NCT06303622	Excluded publication type
NCT03632655 2018	https://clinicaltrials.gov/study/NCT03632655	Excluded publication type
NICE 2019	https://www.ncbi.nlm.nih.gov/books/NBK576979/	Excluded study design
Nordstrom 2021	https://dx.doi.org/10.1016/S1470-2045%2821%2900348-X	Irrelevant population
Nordstrom 2024	https://dx.doi.org/10.1001/jamanetworkopen.2023.54577	Irrelevant population
Panebianco 2018	https://dx.doi.org/10.1016/j.euo.2018.03.008	Irrelevant outcome
Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Porpiglia 2023	https://dx.doi.org/10.23736/S2724-6051.22.05189-8	Irrelevant comparator
Porreca 2020	https://dx.doi.org/10.1097/MD.0000000000022059	Irrelevant population
Prince 2021	https://dx.doi.org/10.2214/AJR.20.25207	Excluded study design
Rabah 2021	https://dx.doi.org/10.15537/smj.2021.42.6.20200771	Irrelevant comparator
Rai 2021	https://dx.doi.org/10.1016/j.euo.2020.12.012	Irrelevant comparator
Rakauskas 2023	https://dx.doi.org/10.1371/journal.pone.0280262	Excluded study design
Russo 2021	https://dx.doi.org/10.1016/j.euo.2021.03.007	Irrelevant comparator
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	Irrelevant population
Schiavina 2021	https://dx.doi.org/10.1016/j.urolonc.2020.10.018	Irrelevant population
Szewczyk-Bieda 2019	https://dx.doi.org/10.1186/s13063-019-3746-0	Irrelevant comparator
Wagensveld 2021	https://doi.org/10.1016/S0302-2838(21)01279-3	Excluded publication type
Wang 2023	https://dx.doi.org/10.1007/s00345-022-04086-0	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.eururo.2018.11.040	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.euo.2019.08.007	Irrelevant population
Wei 2023	https://dx.doi.org/10.1148/radiol.221428	Irrelevant population
Woo 2019	https://dx.doi.org/10.1016/j.euo.2019.05.004	Irrelevant comparator
Yang 2024	https://dx.doi.org/10.1016/j.acra.2024.08.027	Excluded study design
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Excluded study design
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant comparator
Zhang 2022	https://dx.doi.org/10.3389/fsurg.2022.1058288	Irrelevant comparator
Zhu 2018	https://dx.doi.org/10.7150/jca.24690	Irrelevant comparator
Articles from primary studies search and citation search for head-to-head studies		
Agrotis 2023	https://dx.doi.org/10.1002/jcu.23497	Irrelevant comparator
Ahdoot 2020	https://dx.doi.org/10.1056/NEJMoa1910038	Irrelevant comparator

Ahmed 2017	https://doi.org/10.1016/S0140-6736(16)32401-1	Irrelevant intervention
Alqahtani 2021	https://dx.doi.org/10.3390/cancers14010001	Irrelevant comparator
Alqahtani 2022	https://dx.doi.org/10.3390/cancers14010001	Irrelevant comparator
An 2024	https://dx.doi.org/10.1007/s00345-024-04947-w	Irrelevant comparator
Andras 2019	https://dx.doi.org/10.11152/mu-1705	Irrelevant comparator
Araujo 2023	https://dx.doi.org/10.4081/aiua.2023.11830	Irrelevant comparator
Avolio 2023	https://dx.doi.org/10.1007/s00345-023-04480-2	Irrelevant comparator
Bangash 2021	https://dx.doi.org/10.53350/pjmhs2115102625	Irrelevant population
Barrett 2019	https://dx.doi.org/10.1016/j.crad.2019.06.004	Irrelevant comparator
Barrett 2016	https://doi.org/10.1007/s00345-015-1650-0	Irrelevant population
Barth 2021	https://dx.doi.org/10.1016/j.ejro.2021.100332	Irrelevant intervention
Bass 2018	https://dx.doi.org/10.1136/bmjopen-2018-024941	Irrelevant comparator
Bastian-Jordan 2018	https://dx.doi.org/10.1111/1754-9485.12678	Irrelevant comparator
Bhat 2020	https://dx.doi.org/10.1080/13685538.2019.1641796	Irrelevant population
Boeve 2023	https://dx.doi.org/10.1111/bju.16041	Irrelevant intervention
Bonekamp 2019	https://dx.doi.org/10.1007/s00330-018-5751-1	Irrelevant intervention
Borghesi 2021	https://dx.doi.org/10.23736/S2724-6051.20.03758-3	Irrelevant comparator
Bosaily 2020	https://dx.doi.org/10.1016/j.eururo.2020.03.002	Irrelevant intervention
Boschheidgen 2023	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Irrelevant comparator
Bourgeno 2024	https://dx.doi.org/10.1016/j.euo.2024.01.007	Irrelevant comparator
Briggs 2021	https://dx.doi.org/10.1016/j.urology.2021.04.040	Irrelevant population
BrizmohunAppayya 2018	https://dx.doi.org/10.1259/bjr.20170645	Irrelevant population
Camacho 2023	https://doi.org/10.1002/bco2.231	Irrelevant comparator
Cetin 2023	https://dx.doi.org/10.18621/eurj.1198992	Irrelevant population
Chaloupka 2023	https://dx.doi.org/10.1111/bju.16248	Irrelevant comparator
Chandra Engel 2024	https://doi.org/10.1016/j.euo.2024.10.002	Irrelevant comparator
Chau 2018	https://dx.doi.org/10.1016/j.ijso.2018.01.002	Irrelevant population
Chau 2024	https://dx.doi.org/10.1007/s11845-024-03637-1	Irrelevant comparator
Checcucci 2020	https://dx.doi.org/10.23736/S0393-2249.20.03958-2	Irrelevant comparator
Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Irrelevant comparator
Cheng 2021	https://dx.doi.org/10.3389/fonc.2021.643051	Irrelevant comparator
Cheng 2022	https://dx.doi.org/10.1080/08941939.2020.1825884	Irrelevant comparator
Choomark 2023	https://dx.doi.org/10.33192/smj.v75i11.265361	Irrelevant comparator
Connor 2020	https://dx.doi.org/10.1097/JU.0000000000001184	Irrelevant comparator
D'Agostino 2019	https://dx.doi.org/10.4081/aiua.2019.2.87	Irrelevant comparator
D'Agostino 2020	https://dx.doi.org/10.4081/aiua.2019.4.211	Irrelevant comparator
Dahl 2022	https://dx.doi.org/10.1016/j.urolonc.2022.07.011	Irrelevant population
Dahl 2024	https://dx.doi.org/10.1016/j.urolonc.2023.11.004	Irrelevant population
Del Monte 2018	https://dx.doi.org/10.1007/s11547-017-0825-8	Irrelevant comparator
Dell'Oglio 2020	https://dx.doi.org/10.1016/j.euo.2019.03.002	Irrelevant comparator
Demirtas 2019	https://dx.doi.org/10.7759/cureus.6160	Irrelevant comparator
Deniffel 2022	https://dx.doi.org/10.1007/s00330-022-08822-3	Irrelevant population
Dhir 2023	https://dx.doi.org/10.1016/j.urology.2023.04.017	Irrelevant comparator

Diez 2024	https://doi.org/10.1007/s00345-024-05233-5	No comparative data for outcome
Donato 2020	https://dx.doi.org/10.1007/s00345-019-02774-y	Irrelevant comparator
Dragoescu 2023	https://dx.doi.org/10.3390/diagnostics13081373	Irrelevant comparator
Droghetti 2023	https://dx.doi.org/10.1007/s00345-022-04229-3	Irrelevant comparator
Eldred-Evans 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7456	Irrelevant comparator
Elfatairy 2019	https://dx.doi.org/10.1148/rycan.2019190016	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.2967/jnumed.121.263448	Excluded study design
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Irrelevant intervention
Emmett 2023	https://dx.doi.org/10.2967/jnumed.123.266164	Irrelevant intervention
Falagario 2021	https://dx.doi.org/10.1111/iju.14385	Irrelevant comparator
Fleville 2024	https://dx.doi.org/10.1097/JU.0000000000004226	Irrelevant comparator
Freifeld 2019	https://dx.doi.org/10.1016/j.urolonc.2018.10.009	Irrelevant comparator
Fulco 2021	https://dx.doi.org/10.3390/cancers13194833	Irrelevant comparator
Furrer 2022	https://dx.doi.org/10.1111/ans.17713	Irrelevant comparator
Gavin 2020	https://dx.doi.org/10.1016/j.euros.2020.07.001	Irrelevant population
Gayet 2020	https://dx.doi.org/10.1155/2020/4626781	Irrelevant comparator
Gomez-Gomez 2021	https://dx.doi.org/10.3390/diagnostics11081335	Irrelevant comparator
Gorin 2020	https://dx.doi.org/10.1007/s00345-019-02992-4	Irrelevant comparator
Gortz 2022	https://dx.doi.org/10.3390/cancers14040886	Irrelevant population
Grey 2022	https://dx.doi.org/10.1016/S1470-2045(22)00016-X	Irrelevant comparator
Gross 2020	https://dx.doi.org/10.1097/JU.0000000000000534	Irrelevant comparator
Gunzel 2022	https://dx.doi.org/10.1007/s11255-022-03309-y	Irrelevant comparator
Hagens 2022	https://dx.doi.org/10.1016/j.euros.2022.07.006	Irrelevant comparator
Hagens 2022	https://dx.doi.org/10.1016/j.euros.2022.04.001	Irrelevant population
Hansen 2020	https://dx.doi.org/10.1111/bju.14865	Irrelevant population
Hansen 2018	https://dx.doi.org/10.1111/bju.14049	Irrelevant intervention
Henning 2021	https://dx.doi.org/10.1016/j.urolonc.2020.11.018	Irrelevant comparator
Hepp 2022	https://dx.doi.org/10.1007/s00345-022-03991-8	Irrelevant population
Ho 2023	https://dx.doi.org/10.1016/j.urolonc.2023.11.005	Irrelevant population
Hofbauer 2022	https://dx.doi.org/10.1111/bju.15635	Irrelevant population
Hogan 2022	https://dx.doi.org/10.1177/20514158221084820	No comparative data for outcome
Hogan 2024	https://dx.doi.org/10.1177/20514158221084820	Duplicate
Hou 2022	https://dx.doi.org/10.1038/s41391-021-00489-z	Irrelevant comparator
Hsi 2023	https://dx.doi.org/10.1002/bco2.184	No comparative data for outcome
Hsieh 2022	https://dx.doi.org/10.31083/j.jomh1806127	Irrelevant population
Huang 2022	https://dx.doi.org/10.2147/CMAR.S350701	Irrelevant comparator
Hubbard 2021	https://pubmed.ncbi.nlm.nih.gov/34786148/	Irrelevant population
Hung 2024	https://dx.doi.org/10.1016/j.urology.2023.11.039	Irrelevant comparator
Jahnen 2023	https://dx.doi.org/10.1007/s00345-023-04564-z	Irrelevant comparator
Kachanov 2022	https://dx.doi.org/10.1097/JU.0000000000002248	Irrelevant comparator
Kalapara 2022	https://dx.doi.org/10.1016/j.euo.2021.02.006	No comparative data for outcome
Kam 2018	https://dx.doi.org/10.1016/j.prnil.2017.10.003	Irrelevant population

Kasivisvanathan 2024	https://doi.org/10.1016/j.eururo.2024.08.022	Irrelevant comparator
Kato 2021	https://dx.doi.org/10.3390/curroncol28020123	Irrelevant comparator
Kaufmann 2022	https://dx.doi.org/10.1002/pros.24286	Irrelevant population
Khoo 2021	https://dx.doi.org/10.1097/JU.0000000000001476	Irrelevant population
Kim 2021	https://dx.doi.org/10.1007/s00330-020-07167-z	Irrelevant comparator
Kim 2022	https://dx.doi.org/10.1097/JU.0000000000002168	Irrelevant intervention
Kong 2023	https://dx.doi.org/10.1177/20514158211065946	No comparative data for outcome
Kortenbach 2021	https://dx.doi.org/10.1016/j.heliyon.2021.e08325	No comparative data for outcome
Krausewitz 2023	https://dx.doi.org/10.1007/s00345-022-04230-w	Irrelevant comparator
Kuhlmann 2022	https://dx.doi.org/10.1016/j.urolonc.2021.12.016	Irrelevant comparator
Kurokawa 2024	https://dx.doi.org/10.21873/anticanres.16858	Irrelevant comparator
Kwon 2023	https://dx.doi.org/10.1007/s11255-023-03674-2	No comparative data for outcome
Labra 2020	https://dx.doi.org/10.1007/s00261-020-02481-y	Irrelevant comparator
Lahoud 2021	https://dx.doi.org/10.1111/ans.16524	Irrelevant intervention
Lee 2020	https://dx.doi.org/10.1111/bju.15118	Irrelevant intervention
Lee 2021	https://dx.doi.org/10.1016/j.urolonc.2021.02.027	Irrelevant intervention
Lee 2022	https://dx.doi.org/10.1016/j.prnil.2021.08.003	Irrelevant population
Lee 2022	https://dx.doi.org/10.1038/s41391-021-00485-3	Irrelevant comparator
Leow 2023	https://dx.doi.org/10.4103/aja2021128	Irrelevant comparator
Liu 2020	https://dx.doi.org/10.1038/s41391-020-0260-0	Irrelevant comparator
Liu 2021	https://dx.doi.org/10.1259/bjr.20210312	Irrelevant comparator
Liu 2023	https://dx.doi.org/10.1002/jmri.28614	Irrelevant comparator
Lockhart 2022	https://dx.doi.org/10.1177/20514158221085081	No comparative data for outcome
Lombardo 2023	https://dx.doi.org/10.3390/life13081719	Irrelevant comparator
Lopez 2021	https://dx.doi.org/10.1111/bju.15337	No comparative data for outcome
Lovegrove 2020	https://dx.doi.org/10.1097/JU.0000000000000455	Irrelevant intervention
Lughezzani 2019	https://dx.doi.org/10.1016/j.euo.2018.10.001	Irrelevant comparator
Malewski 2023	https://dx.doi.org/10.3390/jcm12175612	Irrelevant comparator
Martin 2023	https://dx.doi.org/10.1007/s00345-023-04386-z	Irrelevant comparator
Mesko 2018	https://dx.doi.org/10.1097/COC.0000000000000308	Irrelevant comparator
Miah 2020	https://dx.doi.org/10.1007/s11701-019-00929-y	Irrelevant population
Mischinger 2018	https://dx.doi.org/10.1111/bju.14089	Irrelevant comparator
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	No comparative data for outcome
Morote 2023	https://dx.doi.org/10.3390/cancers15184543	Irrelevant comparator
Mortezavi 2018	https://dx.doi.org/10.1016/j.juro.2018.02.067	Irrelevant intervention
Neale 2020	https://dx.doi.org/10.1111/bju.15092	Irrelevant population
Noujeim 2023	https://dx.doi.org/10.1038/s41391-022-00620-8	Irrelevant comparator
Novara 2023	https://dx.doi.org/10.1007/s00345-023-04382-3	Irrelevant outcome
Oderda 2024	https://dx.doi.org/10.3390/curroncol31070308	Irrelevant comparator
Oh 2020	https://dx.doi.org/10.4111/icu.2020.61.1.28	Irrelevant intervention
Olivetta 2024	https://dx.doi.org/10.3390/diagnostics14151643	Irrelevant comparator

Osses 2018	https://dx.doi.org/10.1159/000447216	Irrelevant comparator
Pang 2021	https://dx.doi.org/10.12998/wjcc.v9.i36.11183	Irrelevant comparator
Park 2020	https://dx.doi.org/10.3390/jcm9020530	Irrelevant comparator
Patel 2018	https://dx.doi.org/10.1016/j.euo.2018.03.009	Irrelevant comparator
Patel 2022	https://dx.doi.org/10.1097/JU.0000000000002120	Irrelevant comparator
Pepe 2022	https://dx.doi.org/10.21873/anticanres.15785	Irrelevant comparator
Petov 2023	https://dx.doi.org/10.1089/end.2022.0780	Irrelevant comparator
Phelps 2023	https://dx.doi.org/10.1007/s00261-022-03775-z	Irrelevant comparator
Ploussard 2019	https://dx.doi.org/10.1007/s00345-018-2399-z	Excluded study design
Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Pratihar 2023	https://dx.doi.org/10.4103/iju.iju_147_23	Irrelevant comparator
Rachubinski 2022	https://dx.doi.org/10.1097/JU.0000000000002921	Irrelevant population
Radtke 2019	https://dx.doi.org/10.1371/journal.pone.0221350	No comparative data for outcome
Rajendran 2024	https://dx.doi.org/10.1093/bjr/tqad027	No comparative data for outcome
Ruan 2023	https://dx.doi.org/10.1007/s00261-023-03894-1	Irrelevant comparator
Saba 2020	https://dx.doi.org/10.1097/JU.0000000000000622	No comparative data for outcome
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	No comparative data for outcome
Sanguedolce 2024	https://doi.org/10.1016/j.euo.2024.10.006	Irrelevant population
Sathianathen 2018	https://dx.doi.org/10.1038/s41391-018-0065-6	Irrelevant comparator
Sathianathen 2019	https://dx.doi.org/10.1111/bju.14617	Irrelevant comparator
Schelb 2019	https://dx.doi.org/10.1148/radiol.2019190938	Irrelevant outcome
Schmid 2023	https://dx.doi.org/10.1002/pros.24435	No comparative data for outcome
Senoglu 2022	https://dx.doi.org/10.4274/uob.galenos.2021.2021.4.1	Irrelevant comparator
Seref 2022	https://dx.doi.org/10.1002/pros.24255	Irrelevant population
Shefler 2024	https://dx.doi.org/10.1016/j.urolonc.2024.01.026	Irrelevant comparator
Siddiqui 2023	https://dx.doi.org/10.1038/s41391-023-00660-8	Irrelevant outcome
Sigle 2021	https://dx.doi.org/10.3390/cancers13102502	Irrelevant population
Sigle 2022	https://dx.doi.org/10.3390/cancers14215230	Irrelevant population
Sigle 2023	https://dx.doi.org/10.1016/j.euf.2023.01.020	Irrelevant population
Sivaraman 2022	https://dx.doi.org/10.4103/iju.iju_222_21	No comparative data for outcome
Song 2020	https://dx.doi.org/10.1097/JU.0000000000001302	Irrelevant comparator
Stabile 2021	https://dx.doi.org/10.1038/s41391-021-00371-y	Irrelevant comparator
Stavrinides 2023	https://dx.doi.org/10.1148/radiol.220762	Irrelevant population
Stevens 2023	https://dx.doi.org/10.1177/02841851231187135	Irrelevant intervention
Stone 2021	https://dx.doi.org/10.1002/bco2.111	Irrelevant intervention
Sugano 2020	https://dx.doi.org/10.1007/s11255-019-02354-4	Irrelevant comparator
Tae 2018	https://dx.doi.org/10.4111/icu.2018.59.6.363	Irrelevant comparator
Tay 2021	https://dx.doi.org/10.1002/bco2.99	Irrelevant intervention
Thangarasu 2021	https://dx.doi.org/10.2147/RRU.S300868	Irrelevant comparator
Thompson 2023	https://dx.doi.org/10.5152/tud.2023.22221	Irrelevant population
Tomioka 2023	https://dx.doi.org/10.3390/diagnostics13152608	Irrelevant comparator

Tschirdewahn 2021	https://dx.doi.org/10.1016/j.euf.2020.06.020	Irrelevant intervention
Tunc 2023	https://dx.doi.org/10.22037/uj.v20i.7610	Irrelevant comparator
Turkay 2020	https://dx.doi.org/10.1097/RUQ.0000000000000505	Irrelevant comparator
Velarde 2022	https://dx.doi.org/10.1007/s00261-021-03389-x	Irrelevant comparator
Wagaskar 2022	https://dx.doi.org/10.22037/uj.v18i.6852	No comparative data for outcome
Wang 2020	https://dx.doi.org/10.4103/aja.aja_83_19	Irrelevant comparator
Wang 2021	https://dx.doi.org/10.1186/s12894-021-00949-7	Irrelevant comparator
Washino 2018	https://dx.doi.org/10.1186/s12894-018-0361-4	Irrelevant comparator
Wei 2022	https://dx.doi.org/10.1007/s00261-022-03592-4	Irrelevant comparator
Weiser 2023	https://dx.doi.org/10.1002/jmri.28891	No comparative data for outcome
Wenzel 2021	https://dx.doi.org/10.3389/fsurg.2021.633196	Irrelevant intervention
Wong 2024	https://dx.doi.org/10.1016/j.euo.2024.01.002	No comparative data for outcome
Woo 2023	https://dx.doi.org/10.1016/j.euros.2022.11.012	Irrelevant comparator
Wu 2024	https://dx.doi.org/10.1038/s41391-023-00729-4	Irrelevant intervention
Yilmaz 2023	https://dx.doi.org/10.1148/radiol.221309	Irrelevant comparator
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Irrelevant population
Zambon 2024	https://dx.doi.org/10.1038/s41391-023-00770-3	Irrelevant comparator
Zattoni 2023	https://dx.doi.org/10.1007/s00345-023-04578-7	Irrelevant population
Zawaideh 2020	https://dx.doi.org/10.1259/bjr.20200298	Irrelevant comparator
Zhang 2018	https://dx.doi.org/10.1186/s12957-018-1367-9	Irrelevant intervention
Zhang 2019	https://dx.doi.org/10.1016/j.prnil.2018.10.001	Irrelevant comparator
Zhang 2020	https://dx.doi.org/10.1007/s10147-019-01524-9	Irrelevant population
Zhang 2020	https://dx.doi.org/10.21037/tau.2020.02.20	Irrelevant comparator
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant comparator
Zhang 2022	https://dx.doi.org/10.1186/s40644-022-00498-8	Irrelevant comparator
Zhu 2018	https://dx.doi.org/10.1097/MD.0000000000011962	Irrelevant comparator
Articles from Haider 2021 and Drost 2019 systematic reviews		
Alberts 2017	https://doi.org/10.1016/j.eururo.2017.06.019	Irrelevant comparator
Baco 2016	https://doi.org/10.1016/j.eururo.2015.03.041	Irrelevant comparator
Boesen 2018	https://doi.org/10.1001/jamanetworkopen.2018.0219	Irrelevant comparator
Borkowetz 2017	https://doi.org/10.1159/000477263	Irrelevant comparator
Borkowetz 2018	https://doi.org/10.1111/bju.14017	Irrelevant comparator
Castellucci 2017	https://doi.org/10.23736/s0393-2249.17.02845-4	Irrelevant comparator
Chen 2015	https://doi.org/10.3892%2Fetm.2014.2061	Irrelevant comparator
Cool 2016	https://doi.org/10.5489%2Fcuaj.3831	Irrelevant comparator
Delongchamps 2013	https://doi.org/10.1016/j.juro.2012.08.195	Irrelevant comparator
Distler 2017	https://doi.org/10.1016/j.juro.2017.03.130	Irrelevant population
Filson 2016	https://doi.org/10.1002/cncr.29874	Irrelevant comparator
Garcia Bennett 2017	https://doi.org/10.1016/j.diii.2017.06.010	Irrelevant comparator
Grey 2015	https://doi.org/10.1111/bju.12862	Irrelevant population
Gronberg 2018	https://doi.org/10.1016/j.eururo.2018.06.022	Irrelevant comparator
Jambor 2015	https://doi.org/10.1002/jmri.24682	Irrelevant comparator
Jambor 2017	https://doi.org/10.1002/jmri.25641	Irrelevant comparator

Kesch 2017	https://doi.org/10.1159/000458764	No comparative data for outcome
Kim 2017	https://doi.org/10.1016/j.urology.2016.08.074	Irrelevant comparator
Lee 2016	https://doi.org/10.3349/ymj.2016.57.3.565	Irrelevant comparator
Lee 2017	https://doi.org/10.3349%2Fymj.2017.58.5.994	Irrelevant comparator
Muthuveloe 2016	https://doi.org/10.5173/ceju.2016.675	Irrelevant population
Nafie 2014	https://pubmed.ncbi.nlm.nih.gov/28299763/	Irrelevant population
Okcelik 2016	https://doi.org/10.1590/s1677-5538.ibju.2015.0155	Irrelevant comparator
Panebianco 2015	https://doi.org/10.1016/j.urolonc.2014.09.013	Irrelevant comparator
Peltier 2015	https://doi.org/10.1155/2015/571708	Irrelevant comparator
Ploussard 2014	https://doi.org/10.1016/j.eururo.2012.05.049	Irrelevant population
Pokorny 2014	https://doi.org/10.1016/j.eururo.2014.03.002	Irrelevant comparator
Pressier 2019	https://doi.org/10.1016/j.euf.2019.06.015	Irrelevant comparator
Rouvière 2019	https://doi.org/10.1016/s1470-2045(18)30569-2	Irrelevant comparator
Sakar 2019	https://doi.org/10.1177/2051415819889552	Irrelevant comparator
Thompson 2016	https://doi.org/10.1016/j.juro.2015.10.140	No comparative data for outcome
Tonttilla 2016	https://doi.org/10.1016/j.eururo.2015.05.024	Irrelevant comparator
Van der Leest 2019	https://doi.org/10.1016/j.eururo.2018.11.023	Irrelevant comparator
Westoff 2019	https://doi.org/10.1016/j.urolonc.2019.07.004	Irrelevant comparator
Zalesky 2019	https://doi.org/10.5507/bp.2019.050	Irrelevant comparator
Zhang 2017	https://doi.org/10.1007/s11255-016-1484-8	Irrelevant comparator

3.12 Clinical question 8 – Prostate Biopsy PICO 8C

Clinical questions:

8. *For biopsy naïve men with a PI-RADS 4-5 lesion on multiparametric MRI (mpMRI), are targeted biopsies alone acceptable/ reasonable/ adequate? (is a systematic biopsy necessary?)*
9. *For biopsy naïve men with a PI-RADS 3 lesion on mpMRI, are targeted biopsies alone acceptable/ reasonable/ adequate? (is a systematic biopsy necessary?)*

Introduction

Clinical questions 8 and 9 are each addressed by 3 systematic reviews. This is the third systematic review which addresses both clinical questions.

Systematic review report for PICO 8C: Randomised controlled trials comparing complications following a targeted biopsy with those following a systematic and targeted biopsy

Authors

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PICO 8C

This systematic review addresses the following PICOs which are summarised in detail in Tables 1a and 1b.

PICO 8Ca: *For men undergoing a MRI targeted biopsy, does eliminating a systematic biopsy reduce biopsy complications?*

PICO 8Cb: *For men undergoing a MRI targeted biopsy, does reducing the number of systematic biopsy cores reduce biopsy complications?*

Table 1a. *PICO 8Ca components*

Population	*Intervention*	*Comparator*	*Outcomes*	*Study design*
Individuals undergoing biopsy	MRI-targeted biopsy only	MRI-targeted biopsy + ≥ 12 core systematic biopsy OR ≥ 20 core systematic biopsy only	Hospital readmission within 30 days of biopsy Erectile dysfunction at ≥1 year	Randomised controlled trials

Table 1b. *PICO 8Cb components*

Population	*Intervention*	*Comparator*	*Outcomes*	*Study design*
Individuals undergoing biopsy	MRI-targeted biopsy + 12-core systematic biopsy	MRI-targeted biopsy + ≥ 20 core systematic biopsy OR ≥ 20 core systematic biopsy only	Hospital readmission within 30 days of biopsy Erectile dysfunction at ≥1 year	Randomised controlled trials

1. Methods

1.1 Selection criteria

Table 2. *Selection criteria*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	
Study design	RCTs or systematic reviews thereof	
Population	Individuals undergoing prostate biopsy - transperineal or transrectal approach Include men with prior negative biopsy or on active surveillance	
Intervention *PICO 3a*	**MRI-targeted biopsy only** • minimum 2-cores, • any fusion method (software registration, cognitive, in-bore)	Single core targeted biopsy Perilesional biopsies
Intervention *PICO 3b*	**MRI-targeted biopsy** • minimum 2-cores, • any fusion method (software registration, cognitive, in-bore) + **12-core (include < 20 core) systematic biopsy**	Single core targeted biopsy Perilesional biopsies
Comparator *PICO 3a*	**MRI-targeted biopsy** + **≥ 12 core systematic biopsy** OR **≥ 20 core systematic biopsy** alone	Perilesional biopsies The biopsy approach (transrectal or transperineal) used was different from that used for the intervention
Comparator *PICO 3b*	**MRI-targeted biopsy** + **≥ 20 core systematic biopsy** OR **≥ 20 core systematic biopsy** alone	Perilesional biopsies The biopsy approach (transrectal or transperineal) used was different from that used for the intervention
Outcome	**Hospital admission within 30 days** of biopsy (primary outcome) Urinary retention within 30 days of biopsy Infection requiring hospital admission within 30 days of biopsy Sepsis *For men who do not undergo definitive treatment* Erectile dysfunction at 1 year or longer	
Analyses	Per-patient	Per-lesion
Publication date	From 2010 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

MRI = magnetic resonance imaging; RCTs = randomised controlled trials

1.2 Definitions and terminology

For the purposes of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Systematic biopsy refers to a biopsy in which cores are taken from all areas of the prostate according to a template or pattern and includes saturation biopsies.

Targeted biopsy refers to a biopsy in which cores are taken from lesions identified on MRI as suspicious of harbouring significant cancer. Cognitive, software registration or in-bore image fusion techniques are used to identify lesions for biopsy.

- Cognitive image fusion refers to the operator visually fusing MRI images and real time ultrasound pictures.
- Software registration image fusion refers to using software to fuse uploaded MRI images to real time ultrasound.
- In-bore image fusion refers to fusing prior MRI images and a real time MRI during biopsy.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website

- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and as the evidence for mpMRI-targeted biopsy continues to evolve, be based on literature published up until 2022 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

A search for systematic reviews of prostate mpMRI and prostate biopsies published from 2010 onwards in Medline, Embase and Cochrane Systematic Review databases (search strategies in Appendix A) yielded 302 records. Two relevant systematic reviews were identified:

- Haider et al (2021), a systematic review for the Cancer Care Ontario Guideline 27-2 Version 2: *Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer,* captured relevant literature published from 1st May 2013 to 1st September 2020;
- Drost et al (2019) captured relevant literature published from 1st January 1990 to 31st July 2018.

We assessed randomised studies included in the Haider 2021 and Drost 2019 systematic reviews for inclusion in our systematic review, and designed searches to identify randomised controlled trials or systematic reviews thereof published from 2018 onwards. Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations), Embase and Cochrane CENTRAL databases were searched on 30th July 2024 combining text words and database-specific subject headings for prostate cancer, multiparametric MRI and biopsy, and a filter for randomised controlled trials (RCT / CCT - MEDLINE, Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 2024-07-30.) Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st November 2024. The searches were designed to identify potentially relevant trials in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the search is included as Appendix A. Reference lists of recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

The following study characteristics were extracted: Country and year of publication, participant eligibility and age, components of intervention arm, components of comparator arm, and relevant outcomes reported. Effect estimates and 95% confidence intervals were extracted or calculated using relevant reported data. Pooled analyses were planned where there were two or more studies reporting the same outcome.

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias of critical outcomes in each included study (with independent third-reviewer adjudication as needed) using the Cochrane Collaboration Risk of Bias-II tool (Sterne 2019). The overall risk of bias for each outcome was rated low, some concerns or high for the following sources of bias; the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for each outcome determined to be critical by the Biopsy Working Group (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Schunemann 2013) and Schunemann et al 2022, and on guidance for assessing narrative syntheses provided by Murad 2017. Imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. These thresholds were determined by the Biopsy Working Group, and following GRADE guidance provided by Schunemann 2022.

Potential publication bias (or small study effects) was assessed using a Funnel Plot if 10 or more studies. Where there were less than 10 studies, clinical trial registries were searched for potentially relevant trials (see section 1.8 below for search details) commencing between 2015 and 2019 inclusive, that had not been terminated and for which results had not been published suggesting publication bias assuming studies reporting the effects of different biopsy protocols would have published results re biopsy complications and/or cancer detection rates within 5 years of the trial starting and randomised controlled trials comparing MRI targeted biopsies with systematic biopsies would be unlikely prior to 2015.

As per GRADE guidance, randomised controlled trials started with a high level of certainty in the evidence and were to be downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

Definitions of the GRADE ratings of certainty of the overall body of evidence are presented in Appendix B.

1.8 Clinical trial registry searches

Potentially relevant ongoing and unpublished trials were identified from literature searches, recent guidelines and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 29 October 2024. The clinical trial registries were searched with the search terms listed below:

Clinicaltrials.gov using the terms:
“prostate cancer” and “multiparametric MRI” and “biopsy”
“prostate cancer” and “MRI” and “biopsy”
“prostate cancer” and “magnetic resonance imaging” and “biopsy”

International Clinical Trials Registry Platform using the terms:
“prostate cancer” and “multiparametric MRI” and “biopsy”
“prostate cancer” and “MRI” and “biopsy”
“prostate cancer” and “magnetic resonance imaging” and “biopsy”

Australia and New Zealand Clinical Trial Registry using the terms:
“prostate cancer” and “magnetic resonance imaging”
“prostate cancer” and “multiparametric MRI”
“prostate cancer” and “MRI”
“prostate cancer” and “biopsy”

2. Results

2.1 Guidelines searches

One potentially relevant guideline was identified which was based on systematic reviews of the literature published up until 2022 or later. It was not considered for adoption as the systematic reviews were not accessible (Appendix C).

2.2 Literature searches

The systematic search for studies published from 2018 onwards identified 928 unique records to November 1st, 2024 (Figure 1). Of these, 90 full text articles were retrieved for a more detailed evaluation. Three studies published to 2020 included in the Haider 2021 and Drost 2019 systematic reviews were also assessed for inclusion. Two randomised controlled trials reported in two articles met criteria for inclusion in our systematic review: Hugosson 2022 (Goteborg-2 trial), and Dadpour 2023. There were no studies that reported including Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.
The retrieved articles that were not included in this systematic review and the reasons for their exclusion are documented in Appendix D. The main reasons for exclusion were excluded study design or publication type, or irrelevant comparator.

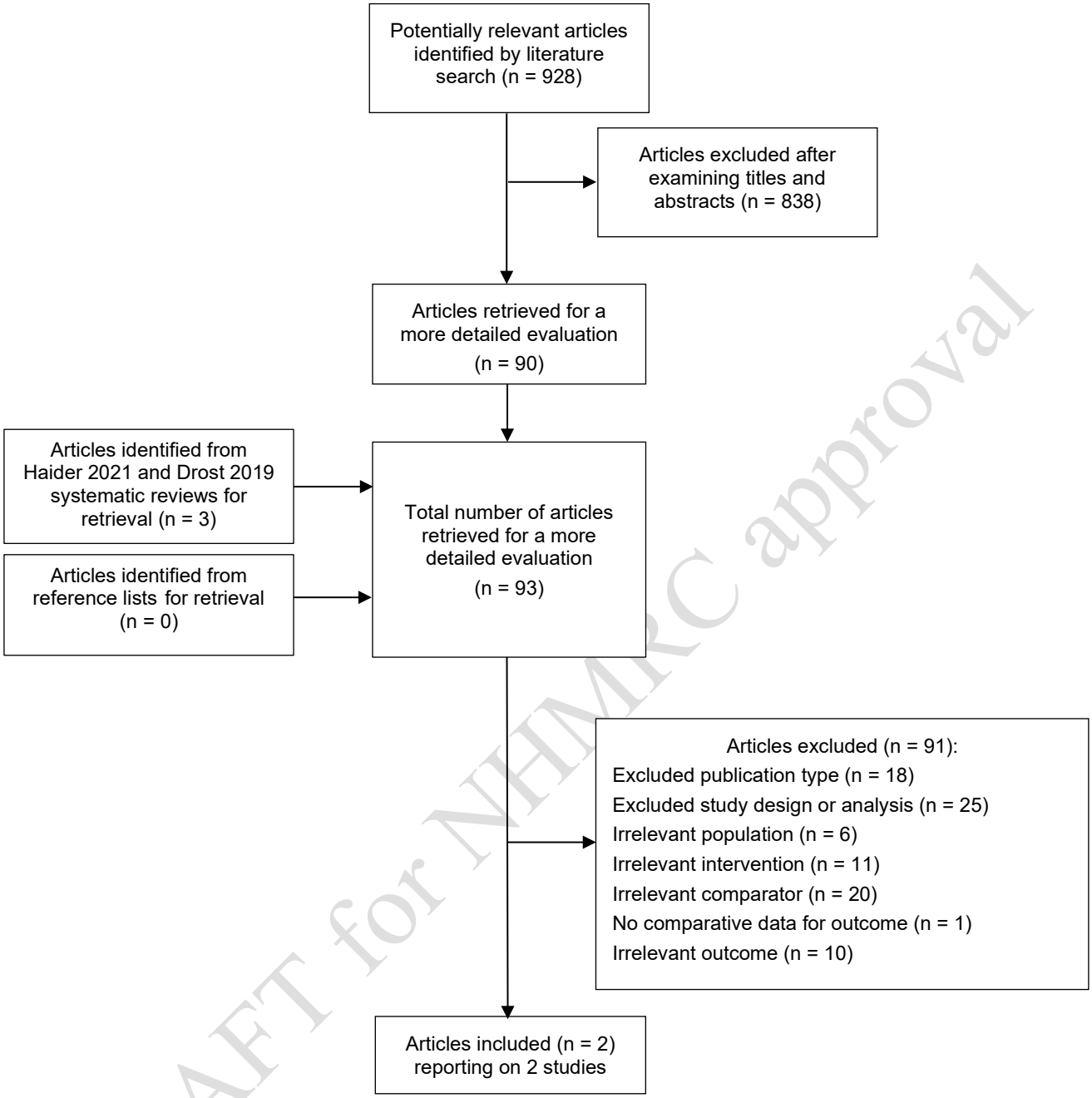

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

2.3 Characteristics of included studies

Table 3. *Study characteristics of included randomised controlled trials of individuals undergoing multiparametric MRI targeted biopsy alone or combined with systematic biopsy to determine the effect of reducing or eliminating systematic biopsy cores on post-biopsy complications*

Study	***Setting and enrolment period***	***Population***	***Intervention arm MRI-TB +/- SB***			***Control arm SB +/- MRI-TB***			***Outcomes of interest***
			N	***MRI-TB***	***SB***	***N***	***MRI-TB***	***SB***	
Hugosson 2022 Sweden *Goteborg-2 trial*	Population-based 2015-2020	Men aged 50-60 years undergoing PSA screening with PSA ≥ 3 ng/mL undergoing mpMRI and prostate biopsy N = 649 % biopsy naïve: NR Age mean: NR PSA ≥ 10 ng/mL: NR	301 (ITT) PI-RADS 3-5: 86.7% 274 (PP)	Transrectal cognitive TRUS fusion MRI-TB **if PIRADS 3-5** 4 cores per lesion N: NR	No transrectal SB unless **PSA ≥ 10 ng/mL Or PIRADS = 5** 10-12 cores N: NR	348 (ITT) PI-RADS 3-5: 39.0% 336 (PP)	Transrectal cognitive TRUS fusion MRI-TB **if PIRADS 3-5** 4 cores per lesion N: NR	Transrectal SB regardless of MRI result 10-12 cores N = 348	Hospitalisation rate at 30 days post-biopsy
Dadpour 2023 Iran	Single centre 2018-2020	Patients aged 40 to 75 years with ≥ 1 PNB (12-core TRUS SB) and PSA > 4 ng/mL undergoing second biopsy N = 105 % biopsy naïve: 0 Age mean: 62.2 years PSA level mean: 11.8 ng/mL	53	Transrectal software registration image TRUS fusion MRI-TB of PIRADS 2-5 lesions Cores per lesion NR Mean 4.6 cores per patient N = 53	Transrectal SB 12 cores N = 53	52	None No MRI or TB N = 0	Transrectal TRUS SB 20 cores N = 52	Hospitalisation for biopsy complications

ITT = intention to treat; MRI-TB = multiparametric MRI targeted biopsy; NR = not reported; PIRADS = Prostate imaging reporting and data system; PNB = prior negative biopsy; PSA = prostate specific antigen; PP = per protocol; RCT = randomised controlled trial; SB = systematic biopsy; TRUS = transrectal ultrasound-guided.

2.4 Results by outcome of interest

Results related to the detection of

Hospital admission within 30 days of biopsy (primary outcome) – Table 4

Erectile dysfunction at 1 year or longer – no results

Results for hospital admission within 30 days of biopsy

Table 4: *Hospitalisation rate within 30 days of biopsy*

Study	***Population***	***Outcome***	***Intervention arm TB +/- SB***		***Control arm SB +/- TB***		***Risk ratio* (95% CI)***
			Biopsy protocol	***Hospitalisation rate*** *Per 100 (n/N)*	***Biopsy protocol***	***Hospitalisation rate*** *Per 100 (n/N)*	
Hugosson 2022 (GOTEBORG-2) Sweden	PSA ≥ 3 ng/ml	Hospitalisations within 30 days of biopsy	TR TB (all) +/- 10-12-core SB (< 50%)	0.33 (1/301) (Hospitalisation for urosepsis)	TR 10-12-core SB (all) +/-TB (< 50%?)	1.15 (4/348) (Hospitalisations for urosepsis (2), pneumonia and acute hypertension)	0.29 (0.03, 2.57)
Dadpour 2023 Iran	≥ 1 PNB PIRADS 2-5	Biopsy complications requiring hospitalisation	TR TB + 12-core SB Mean cores = 16.6	1.89 (1/53) (Hospitalisation for fever)	TR 20-core SB Mean cores = 20	1.92 (1/52) (Hospitalisation for fever)	0.98 (0.06, 15.28)

CI = confidence interval; PIRADS = Prostate imaging reporting and data system; PNB = prior negative biopsy; PSA = prostate specific antigen; SB = systematic biopsy; TB = targeted biopsy; TR = transrectal

**Risk ratio calculated by technical team using tool at https://sample-size.net/risk-ratio/*

2.5 Risk of bias

The results of the risk of bias assessments for the included studies are shown in Table 5.

Table 5. *Risk of bias assessments for included studies of randomised controlled trials studies using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) (Sterne 2019)*

Study	*Source of bias*					*Overall risk of bias*
	Randomisation process	*Deviations from intended interventions*	*Missing outcome data*	*Measurement of the outcome*	*Selection of the reported result*	
Hugosson 2022	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Dadpour 2023	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns

Key to overall rating
Low risk of bias: "Low" for all domains
Some concerns regarding risk of bias: "Some concerns" but not "high" for one or more domains
High risk of bias: "High" for one or more domains

3. GRADE Certainty of the evidence

Hospitalizations within 30 days of biopsy – assessments are shown in Table 6 for PICO 8Ca and Table 7 for PICO 8Cb

Table 6. *GRADE assessment of the certainty of the evidence for the outcome of hospitalisations within 30 days of biopsy from randomised controlled trials comparing targeted biopsy with systematic biopsy with or without targeted biopsy (PICO8Ca).*

GRADE domain	Rating	Reason for rating	Certainty of evidence
Targeted biopsy vs 10-12-core systematic biopsy +/- targeted biopsy			
Risk of bias	No serious concerns	For a single trial reporting this outcome, none of the sources of bias were judged to be at high risk of bias. There were some concerns regarding the risk of bias due to randomisation, deviations from intended interventions and missing outcome data, but these were not considered likely to have caused major distortions to the results for this PICO.	*LOW*
Indirectness	Very serious concerns	In the intervention arm those with a PIRADS of 5 and those with a PSA level ≥ 10 ng/ml underwent a systematic biopsy as well as a targeted biopsy so a systematic biopsy was not entirely eliminated and thus the results were not directly relevant. In addition, a transrectal approach was used and a 10- to 12-core systematic biopsy was performed in the control arm. However, in Australia it is more likely that a transperineal approach, which has a lower risk of infections, will be used, and that over 20 cores will be taken for a systematic biopsy. Consequently, the comparison and its results may not be directly relevant to the Australian context.	
Imprecision	No serious concerns	Based on a risk ratio of 0.29 with 95% confidence interval of 0.03 to 2.57, in a population of 1000 men undergoing biopsy, performing a targeted biopsy only rather a systematic biopsy with or without targeted biopsy is estimated to result in 8 less (11 less, 18 more) hospitalisations within 30 days of biopsy. Using a MCID of 50 hospitalisations within 30 days of biopsy/1000 and thresholds for moderate and large effects of 100 hospitalisations/1000 and 200 hospitalisations/1000, the absolute difference between the two arms was not clinically important, and its 95% CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any relevant trials starting between 2015 and 2019 inclusive with unpublished results.	

CI = confidence interval; MCID = minimal clinically important difference; PIRADS = Prostate Image-Reporting and Data System; PSA = prostate specific antigen

Table 7. *GRADE assessment of the certainty of the evidence for the outcome of hospitalszations within 30 days of biopsy from randomised controlled trial evidence comparing targeted biopsy and < 20-core systematic biopsy with ≥ 20-core systematic biopsy with or without targeted biopsy.*

GRADE domain	*Rating*	*Reason for rating*	*Certainty of evidence*
Targeted biopsy + 12-core systematic biopsy vs 20-core systematic biopsy			
Risk of bias	No serious concerns	For a single trial reporting hospitalisations with fever following biopsy, none of the sources of bias were judged to be at high risk of bias. There were some concerns regarding the risk of bias due to randomisation, deviations from intended interventions, missing outcome data, outcome measurement and selection of reported outcomes arising in many cases from an absence of reported details. None of these sources of bias were considered likely to have caused major distortions to the results for this PICO.	*VERY LOW*
Indirectness	Serious concerns	In this study it is unclear as to how long participants were followed up post biopsy for any hospitalisations or hospitalisations due to biopsy complications. In this study a transrectal approach was used rather than a transperineal approach, the latter of which has a lower risk of infection and is commonly used in Australia. Consequently the outcome may not be directly relevant to the PICO or the Australian context.	
Imprecision	Extremely serious concerns	Based on a risk ratio of 0.98 with 95% confidence interval of 0.06 to 15.28, in a population of 1000 men undergoing biopsy, performing a targeted biopsy and a 12-core systematic biopsy rather than a 20-core biopsy is estimated to result in 0.4 less (18 less, 274 more) hospitalisations for biopsy complications. Using a MCID of 50 hospitalisations within 30 days of biopsy/1000 and thresholds for moderate and large effects of 100 hospitalisations/1000 and 200 hospitalisations/1000, the absolute difference between the two arms was not clinically important, but its 95% CI crossed the thresholds for small, moderate and large increases.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any relevant trials starting between 2015 and 2019 inclusive with unpublished results.	

CI = confidence interval; MCID = minimal clinically important difference

4. Summary of findings

Table 8. *Summary of findings for targeted biopsy vs systematic biopsy with or without targeted biopsy (PICO 8Ca).*

Outcome (MCID)	Time frame	RCTs (N)	Participants (N)	Study results and measurements	Absolute effect estimates				Certainty of evidence (GRADE)	Plain text summary
					Metric	Systematic biopsy +/- targeted biopsy	Targeted biopsy (95% CI)	Difference (95% CI)		
Targeted biopsy vs 10-12-core systematic biopsy +/- targeted biopsy										
Post biopsy hospitalisation (50/1000)	30 days	1	649	RR: 0.29 (0.03, 2.57)	Hospitalisations per 1000	11.5	3.3 (0.3, 29.6)	8 less (11 less, 18 more)	Low[1]	In a population of men undergoing biopsy, undertaking a targeted biopsy only rather than a systematic biopsy as well as a targeted biopsy may result in a clinically **unimportant^** difference in the number of hospitalisations within 30 days of biopsy.

CI = confidence interval; MCID = minimally important difference; RCT = randomised controlled trial; RR = risk ratio
[1] Downgraded by two levels due to very serious concerns re indirectness
^ Using thresholds of 50, 100 and 200 hospitalisations within 30 days of biopsy /1000 for small (minimal clinically important difference), moderate and large effects

Table 9. *Summary of findings for targeted biopsy and < 20-core systematic biopsy vs ≥ 20-core systematic biopsy (PICO 8Cb).*

Outcome (MCID)	Time frame	RCTs (N)	Participants (N)	Study results and measurements	Absolute effect estimates				Certainty of evidence (GRADE)	Plain text summary
					Metric	20-core systematic biopsy	Targeted biopsy + 12-core systematic biopsy (95% CI)	Difference (95% CI)		
Targeted biopsy + 12-core systematic biopsy vs 20-core systematic biopsy										
Hospitalisation for post biopsy fever (50/1000)	NR	1	105	RR: 0.98 (0.06, 15.28)	Hospitalisations per 1000	19.2	18.8 (1.2, 293.4)	0.4 less (18 less, 274 more)	Very low[1]	In a population of men undergoing biopsy, we are uncertain as to whether undertaking a targeted biopsy and a 12-core systematic biopsy rather than a 20-core systematic biopsy will result in a clinically **unimportant^** difference in the number of hospitalisations due to biopsy complications.

CI = confidence interval; MCID = minimally important difference; RCT = randomised controlled trial; RR = risk ratio
[1] Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness
^ Using thresholds of 50, 100 and 200 hospital admissions within 30 days of biopsy /1000 for small (minimal clinically important difference), moderate and large effects

5. Ongoing clinical trials

Two potentially relevant ongoing trial protocols were identified by searches of clinical trial registries or literature searches.

Table 10. *Summary of potentially relevant ongoing randomised controlled trials comparing biopsy protocols with lower numbers of biopsy cores which include a targeted biopsy with a systematic biopsy of ≥ 20 cores with or without MRI-targeted biopsy*

Study ID Publications	Study name, location and study design	Start date	Planned completion date	Population	Intervention	Comparator	Outcomes
NCT04685928	Extended Systematic Versus Mri-Assisted pRostate Transperineal Biopsy (SMART) trial Hong Kong RCT – 2 arms	2021 Recruiting	2025	Biopsy-naïve men aged ≥18 years with clinical suspicion of prostate cancer based on elevated PSA (4-20 ng/mL) +/- abnormal DRE	**TB + 12-core SB** (MRI) If PIRADS score 3-5, transperineal MRI-targeted biopsy (3-4 cores) + 12-core systematic biopsy (sparing MRI targets) If PIRADS score 1-2, no biopsy	**24-core SB** (No mpMRI) Transperineal 24-core systematic biopsy for all men	*Primary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection *Secondary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection of MRI-targeted biopsy only vs systematic biopsy only Clinically insignificant prostate cancer (ISUP Grade 1) detection Biopsies avoided among mpMRI negative men Maximum cancer core length **Adverse events at 30 days post biopsy** Health-related quality of life Cost per diagnosis of cancer
NCT04993508	Randomized Prospective Multi Center Cohort Study for Primary Diagnosis of Clinically Significant Prostate Cancer with Combination of PSA/DRE and Multi Parametric Magnetic Resonance Imaging (PRIMA)	2026 Not yet recruiting	2028	Biopsy-naïve men aged 50 to 75 years with mpMRI PIRADS 4-5, or PIRADS 3 and PSAD > 0.15 ng/mL^2 undergoing prostate biopsy under local or general anaesthesia. mpMRI indication: Elevated PSA (≥4 ng/mL) and/or cancer suspicious DRE	**TB only** Transperineal or transrectal TRUS fusion MRI-targeted biopsy (maximum 6 cores from 3 lesions)	**TB + 12-core SB** Transperineal or transrectal TRUS fusion MRI-targeted biopsy (maximum 6 cores from 3 lesions) + 12-core systematic biopsy	*Primary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection Clinically insignificant prostate cancer (ISUP Grade 1) detection *Secondary* **Complications rate at 30 days post-biopsy** Number of biopsies avoided Detection rate of MRI in-bore biopsy Detection rate of bpMRI Number of PIRADS upgrades and downgrades

	Germany RCT – 2 arms						Patient-reported outcomes including: Pain score Quality of life

DRE = digital rectal examination; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric magnetic resonance imaging; PIRADS = Prostate Image-Reporting and Data System; RCT = randomised controlled trial; TRUS = transrectal ultrasound

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Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019 Apr 25;4(4):CD012663.

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APPENDICES

Appendix A: Literature search strategies

A.1 Search strategies for systematic reviews published 2010 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2010 -Current"
20	(Systematic* adj3 review*).tw.
21	(meta-analys* or meta analys*).tw.
22	20 or 21
23	19 and 22
24	remove duplicates from 23

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2010 and Jan 2025, in Cochrane Reviews (Word variations have been searched)

A.2 Search strategies for primary studies published 2018 onwards

Databases: Medline, Embase and Cochrane Central Register of Controlled Trials databases (via Ovid platform)

#	Searches
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
21	Randomized Controlled Trial/
22	exp Randomized Controlled Trials as Topic/
23	"Randomized Controlled Trial (topic)"/
24	Controlled Clinical Trial/
25	exp Controlled Clinical Trials as Topic/
26	"Controlled Clinical Trial (topic)"/
27	Randomization/
28	Random Allocation/
29	Double-Blind Method/
30	Double Blind Procedure/
31	Double-Blind Studies/
32	Single-Blind Method/
33	Single Blind Procedure/
34	Single-Blind Studies/
35	Placebos/
36	Placebo/
37	Control Groups/
38	Control Group/
39	(random* or sham or placebo*).ti,ab,hw,kf.
40	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
41	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
42	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
43	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
44	allocated.ti,ab,hw.
45	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
46	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
47	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
48	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
49	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
50	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
51	or/20-50
52	19 and 51
53	remove duplicates from 52

Appendix B: GRADE assessment of the certainty of the evidence

Grade	*Definition*
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reportedly based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	The systematic reviews were not accessible

Appendix D: Excluded Studies

Article/Record	*DOI*	*Reason for exclusion*
Articles from primary studies search and citation searching		
Ahlberg 2019	https://dx.doi.org/10.1136/bmjopen-2018-027860	Irrelevant intervention
Alberts 2019	https://dx.doi.org/10.1016/j.eururo.2018.07.031	Excluded study design
Alkema 2022	https://dx.doi.org/10.1016/j.euros.2022.08.005	Excluded study design
Alterbeck 2024	https://dx.doi.org/10.1111/bju.16143	Excluded study design
Amin 2020	https://dx.doi.org/10.1111/bju.14999	Excluded study design
Arsov 2022	https://dx.doi.org/10.1002/ijc.33940	Irrelevant intervention
Auvinen 2024	https://dx.doi.org/10.1001/jama.2024.3841	Irrelevant intervention
Baccaglini 2021	https://dx.doi.org/10.1016/j.clgc.2020.06.008	Excluded study design
Bates 2023	https://doi.org/10.1016/S0302-2838(23)00144-6	Excluded publication type
Bjornebo 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.7131	Irrelevant intervention
Boschheidgen 2024	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Excluded study design
Bratt 2019	https://dx.doi.org/10.1016/j.eururo.2019.02.035	Irrelevant population
Bryant 2023	https://dx.doi.org/10.1111/bju.15978	Irrelevant comparator
Checcucci 2024	https://doi.org/10.1016/S0302-2838(22)00538-3	Excluded publication type
Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Excluded study design
Checcucci 2023	https://doi.org/10.21873/anticanres.16021	Excluded publication type
Checcucci 2022	https://doi.org/10.1097/JU.0000000000002555.11	Excluded publication type
Checcucci 2022	https://doi.org/10.1016/S2666-1683(22)01175-2	Excluded publication type
Chen 2018	https://dx.doi.org/10.1016/j.ajur.2017.07.001	Excluded study design
ChiCTR2000036915 2020	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000036915	Excluded publication type/ Irrelevant comparator
Choi 2019	https://dx.doi.org/10.1016/j.clgc.2018.09.007	Excluded study design
DRKS00032422 2023	https://drks.de/search/en/trial/DRKS00032422	Excluded publication type/ Irrelevant comparator
Eineluoto 2018	https://dx.doi.org/10.1016/j.euo.2018.02.005	Excluded study design
Eklund 2021	https://dx.doi.org/10.1056/NEJMoa2100852	Irrelevant comparator

Elwenspoek 2019	https://dx.doi.org/10.1001/jamanetworkopen.2019.8427	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Excluded study design
Ettala 2022	https://dx.doi.org/10.1136/bmjopen-2021-053118	Irrelevant intervention
Exterkate 2020	https://dx.doi.org/10.1016/j.euo.2019.06.005	Irrelevant outcome
Exterkate 2023	https://dx.doi.org/10.1111/bju.15876	Irrelevant outcome
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	Irrelevant comparator
Ghai 2024	https://dx.doi.org/10.1148/radiol.231948	Irrelevant population
Guo 2024	https://dx.doi.org/10.1186/s13244-024-01699-4	Excluded study design
Hamid 2019	https://dx.doi.org/10.1016/j.eururo.2018.08.007	Excluded study design
He 2021	https://dx.doi.org/10.1136/bmjopen-2020-041427	Excluded publication type
Hu 2020	https://dx.doi.org/10.1007/s00261-019-02370-z	Irrelevant comparator
Hugosson 2019	https://doi.org/10.1016/S1569-9056(19)31108-X	Excluded publication type
Israel 2022	https://dx.doi.org/10.1111/bju.15562	Excluded study design
ISRCTN60263108 2022	https://www.isrctn.com/ISRCTN60263108	Excluded publication type/ Irrelevant comparator
Izadpanahi 2021	https://dx.doi.org/10.1038/s41391-021-00366-9	Irrelevant comparator
Jahnen 2024	https://doi.org/10.1016/S0302-2838(24)00876-5	Excluded publication type
Jahnen 2023	https://doi.org/10.1016/S0302-2838(23)00355-X	Excluded publication type
Jiang 2024	https://dx.doi.org/10.1016/j.euo.2023.12.002	Irrelevant comparator
Kasivisvanathan 2018	https://dx.doi.org/10.1056/NEJMoa1801993	Irrelevant comparator
Kasivisvanathan 2019	https://dx.doi.org/10.1016/j.eururo.2019.04.043	Irrelevant comparator
Kasivisvanathan 2022	https://dx.doi.org/10.1371/journal.pone.0263345	Irrelevant comparator
Kelly 2023	https://dx.doi.org/10.1016/j.euros.2023.05.002	Excluded study design
Klotz 2020	https://dx.doi.org/10.1016/j.eururo.2019.10.007	Irrelevant outcome
Klotz 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7589	Irrelevant comparator
Klotz 2022	https://dx.doi.org/10.1016/j.cct.2021.106618	Irrelevant intervention
Klotz 2024	https://dx.doi.org/10.1016/j.euo.2023.09.013	Irrelevant outcome
Kohestani 2021	https://dx.doi.org/10.1080/21681805.2021.1881612	Irrelevant population
Kruger-Stokke 2021	https://dx.doi.org/10.3389/fonc.2021.745657	Irrelevant outcome
Liu 2024	https://dx.doi.org/10.1136/bmjopen-2023-080593	Excluded study design
Luzzago 2021	https://dx.doi.org/10.1038/s41391-020-00290-4	Excluded study design
Mian 2024	https://dx.doi.org/10.1097/JU.0000000000003979	Excluded study design
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	Excluded study design
Morote 2024	https://dx.doi.org/10.3390/cancers16132306	Excluded study design
NCT06303622 2024	https://clinicaltrials.gov/study/NCT06303622	Excluded publication type/ Irrelevant comparator
NCT04953351 2021	https://clinicaltrials.gov/study/NCT04953351	Excluded publication type/ Irrelevant comparator
NCT04993508 2021	https://clinicaltrials.gov/study/NCT04993508	Excluded publication type/ Irrelevant comparator
NCT03572946 2018	https://clinicaltrials.gov/study/NCT03572946	Excluded publication type/ Irrelevant comparator
NCT03632655 2018	https://clinicaltrials.gov/study/NCT03632655	Excluded publication type/ Irrelevant comparator
NICE 2019	https://www.ncbi.nlm.nih.gov/books/NBK576979/	Excluded study design
Nordstrom 2021	https://dx.doi.org/10.1016/S1470-2045%2821%2900348-X	Irrelevant population
Nordstrom 2024	https://dx.doi.org/10.1001/jamanetworkopen.2023.54577	Irrelevant outcome
Panebianco 2018	https://dx.doi.org/10.1016/j.euo.2018.03.008	Irrelevant outcome

Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Porpiglia 2023	https://dx.doi.org/10.23736/S2724-6051.22.05189-8	Irrelevant intervention
Porreca 2020	https://dx.doi.org/10.1097/MD.0000000000022059	Irrelevant outcome
Prince 2021	https://dx.doi.org/10.2214/AJR.20.25207	Excluded study design
Rabah 2021	https://dx.doi.org/10.15537/smj.2021.42.6.20200771	Irrelevant comparator
Rai 2021	https://dx.doi.org/10.1016/j.euo.2020.12.012	Irrelevant comparator
Rakauskas 2023	https://dx.doi.org/10.1371/journal.pone.0280262	Excluded study design
Russo 2021	https://dx.doi.org/10.1016/j.euo.2021.03.007	Irrelevant comparator
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	Irrelevant outcome
Schiavina 2021	https://dx.doi.org/10.1016/j.urolonc.2020.10.018	Irrelevant comparator
Szewczyk-Bieda 2019	https://dx.doi.org/10.1186/s13063-019-3746-0	Irrelevant comparator
Wagensveld 2021	https://doi.org/10.1016/S0302-2838(21)01279-3	Excluded publication type
Wang 2023	https://dx.doi.org/10.1007/s00345-022-04086-0	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.eururo.2018.11.040	No comparative data for outcome
Wegelin 2019	https://dx.doi.org/10.1016/j.euo.2019.08.007	Irrelevant outcome
Wei 2023	https://dx.doi.org/10.1148/radiol.221428	Irrelevant population
Woo 2019	https://dx.doi.org/10.1016/j.euo.2019.05.004	Irrelevant comparator
Yang 2024	https://dx.doi.org/10.1016/j.acra.2024.08.027	Excluded study design
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Excluded study design
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant intervention
Zhang 2022	https://dx.doi.org/10.3389/fsurg.2022.1058288	Irrelevant intervention
Zhu 2018	https://dx.doi.org/10.7150/jca.24690	Irrelevant comparator
Articles from Haider 2021 and Drost 2019 systematic reviews		
Baco 2016	https://doi.org/10.1016/j.eururo.2015.03.041	Irrelevant comparator
Panebianco 2015	http://dx.doi.org/10.1016/j.urolonc.2014.09.013, 17.e1-7	Irrelevant intervention
Tontilla 2016	https://doi.org/10.1016/j.eururo.2015.05.024	Irrelevant comparator

3.13 Clinical question 9 – Prostate biopsy PICO 9A

Clinical question 9: *For biopsy naïve men with a PI-RADS 3 lesion on multiparametric MRI (mpMRI) are targeted biopsies alone acceptable/ reasonable/ adequate? (is a systematic biopsy necessary?)*

Introduction

This is the first of three systematic reviews which address Clinical question 9.

Systematic review report for PICO 9A: Comparisons of prostate cancer detection by mpMRI targeted biopsy compared to combined systematic and targeted biopsy

Authors

Chelsea Carle, Karen Chiam, Susan Yuill, Michael David, Suzanne Hughes

PICO

This systematic review addresses the following PICO which is summarised in detail in Table 1.

PICO 9A. *For biopsy naïve men with a PI-RADS 3 lesion on mpMRI how do the rates of clinically significant and insignificant cancers detected using a targeted biopsy alone compare with those using a targeted biopsy together with a 20 or more-core systematic biopsy?*

Table 1. *PICO components*

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Biopsy naïve individuals with a PI-RADS 3 lesion on mpMRI	MRI-targeted biopsy only	≥ 20 core systematic biopsy +/- MRI-targeted biopsy	Detection of • ≥ ISUP grade 2 prostate cancer • ISUP grade 1 prostate cancer • ≥ ISUP grade 3 prostate cancer	Randomised controlled trial or Fully paired comparison

ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PI-RADS = Prostate Image-Reporting and Data System

1. Methods

1.1 Selection criteria

Table 2. *Selection criteria*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	
Study design	Cross-sectional head-to-head (fully paired) studies, or Randomised controlled trials or Systematic reviews thereof	
Population	Biopsy naïve individuals with a PI-RADS or Likert score 3 lesion on mpMRI	> 10% of population have undergone prior biopsy and outcomes not stratified for biopsy-naïve patients. Prostate cancer patients (restricted to radical prostatectomy specimens) Not 5-point Likert scale.
Intervention	**MRI-targeted biopsy only** • minimum 2-cores, • any fusion method (software registration, cognitive, in-bore) • transperineal or transrectal approach	Single core targeted biopsy Perilesional biopsies
Comparator	≥ 20 core systematic biopsy • includes template biopsies, • transperineal or transrectal approach +/- MRI-targeted biopsy	Systematic or template biopsy < 20 cores. Systematic biopsy excludes regions sampled by targeted biopsy Biopsy approach differed from that used for the intervention
Outcome	Detection of: **ISUP grade ≥ 2 (primary outcome)**, or ISUP grade ≥ 3, or ISUP grade 1	ISUP grade ≥ 2 combined with a subgroup of ISUP grade 1 for example • Max CCL ≥5 mm for Gleason score 6 disease
Analyses	Per-patient	Per-lesion
Publication date	From 2010 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

CCL = cancer core length; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PI-RADS = Prostate Image-Reporting and Data System

1.2 Definitions and terminology

For the purposes of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).

ISUP grade ≥ 3 prostate cancer is prostate cancer scored as Gleason Score 7(4+3) or higher on histopathological findings (Epstein 2016).

ISUP grade 1 prostate cancer is prostate cancer scored as Gleason Score 6(3+3) on histopathological findings (Epstein 2016).

Multi-parametric MRI (mpMRI) refers to an imaging protocol used to detect and characterise tissue abnormalities to determine the presence and severity of cancer. Prostate mpMRI acquisition includes T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging.

Systematic biopsy refers to a biopsy in which cores are taken from all areas of the prostate according to a template or pattern and includes saturation biopsies.

Targeted biopsy refers to a biopsy in which cores are taken from lesions identified on MRI as suspicious of harbouring significant cancer. Cognitive, software registration or in-bore image fusion techniques are used to identify lesions for biopsy.

- Cognitive image fusion refers to the operator visually fusing MRI images and real time ultrasound pictures.
- Software registration image fusion refers to using software to fuse uploaded MRI images to real time ultrasound.
- In-bore image fusion refers to fusing prior MRI images and a real time MRI during biopsy.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website

- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and as the evidence for mpMRI-targeted biopsy continues to evolve, be based on literature published up until 2022 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

A search for systematic reviews of prostate mpMRI published from 2010 onwards in Medline, Embase and Cochrane Systematic Review databases (search strategy in Appendix A) yielded 302 records. Two relevant systematic reviews were identified:

- Haider et al (2021), a systematic review for the Cancer Care Ontario Guideline 27-2 Version 2: *Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer*, captured relevant literature published from 1st May 2013 to 1st September 2020
- Drost et al (2019) captured relevant literature published from 1st January 1990 to 31st July 2018

We assessed studies included in the Haider 2021 and Drost 2019 systematic reviews for inclusion in our systematic review, and designed separate searches to identify randomised controlled trials and head-to-head (paired) studies or systematic reviews thereof published from 2018 onwards. Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations), Embase and Cochrane CENTRAL databases were searched initially on 6th December 2023 combining text terms and database-specific subject headings for prostate cancer, multiparametric MRI and biopsy, and a filter for randomised controlled trials (RCT / CCT - MEDLINE, Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 2024-07-30.)

Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st November 2024. The searches were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the searches is included as Appendix A. Reference lists of recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

The following study characteristics were extracted: Country and year of publication, study setting and period, participant eligibility and age, details of mpMRI, MRI-targeted biopsy and systematic biopsy, and relevant outcomes reported. Cancer undetected by MRI-targeted biopsy, and relative detection of MRI-targeted biopsy compared to combined systematic and MRI-targeted biopsy were calculated. Pooled analyses were planned where there were two or more studies reporting the same outcome. The *meta* command in Stata Version 18.0 (StataCorp 2023) was used to generate study-specific and pooled relative sensitivity of MRI-targeted biopsy compared to combined systematic and MRI-targeted biopsy to detect clinically significant prostate cancer, and associated 95% confidence intervals, using a Tukey-Freeman proportion random-effects model. Sensitivity analysis using the *leaveoneout* command were planned for outlying study estimates. Forest plots were obtained to present the results graphically.

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias of outcomes in each included study, with independent third-reviewer adjudication as needed. For randomised studies, risk of bias assessment was planned using the Cochrane Collaboration Risk of Bias-II tool (Sterne 2019), and for head-to-head (paired) studies, using a modified version of the Quality of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool (Whiting 2011). The overall risk of bias of studies was rated low, moderate, high or unclear.

1.7 GRADE assessment of the certainty of the evidence

GRADE assessments were planned to assess the certainty of the body of evidence for each outcome. (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence was rated *high*, *moderate*, *low* or *very low* based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Schunemann 2013), Schunemann 2020a, Schuneman 2020b and Schunemann et al 2022. Imprecision was assessed in the context of whether there was a clinically important decrease using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. These thresholds were predetermined by the Biopsy Working Group following GRADE guidance provided by Schunemann 2022. Potential publication bias (or small study effects) was assessed using a Funnel Plot if 10 or more studies. Where there were less than 10 studies: for randomised evidence, clinical trial registries were searched for potentially relevant trials (see Section 1.8 below for search details) that had planned completion dates prior to 2020 (5 or more years ago), that had not been terminated and for which results had not been published suggesting publication bias; and for evidence from fully paired studies sources of funding and conflicts of interest were considered. As per GRADE guidance, studies started with a high level

of certainty in the evidence and downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

1.8 Clinical trial registry searches

Potentially relevant ongoing and unpublished trials were identified from literature and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 29 October 2024. The clinical trial registries were searched with the search terms listed below:

Clinicaltrials.gov using the terms:

"prostate cancer" and "multiparametric MRI" and "biopsy"

"prostate cancer" and "MRI" and "biopsy"

"prostate cancer" and "magnetic resonance imaging" and "biopsy"

International Clinical Trials Registry Platform using the terms:

"prostate cancer" and "multiparametric MRI" and "biopsy"

"prostate cancer" and "MRI" and "biopsy"

"prostate cancer" and "magnetic resonance imaging" and "biopsy"

Australia and New Zealand Clinical Trial Registry using the terms:

"prostate cancer" and "magnetic resonance imaging"

"prostate cancer" and "multiparametric MRI"

"prostate cancer" and "MRI"

"prostate cancer" and "biopsy"

2. Results

2.1 Guidelines searches

One potentially relevant guideline was identified which was based on systematic reviews of the literature published up until 2022 or later. It was not considered for adoption as the systematic reviews were not accessible (Appendix C).

2.2 Literature searches

The systematic search for studies published from 2018 onwards identified 5908 unique records to November 1st, 2024 (Figure 1). Of these, 284 full text articles were retrieved for a more detailed evaluation. 36 studies published to 2020 included in the Haider 2021 and Drost 2019 systematic reviews, and one article identified in a reference list were also assessed for inclusion. Three head-to-head studies met criteria for inclusion in our systematic review: Hansen 2018, Mortezavi 2018, and Bonekamp 2019. No randomised controlled trials met inclusion criteria. There were no studies that included Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.

The retrieved articles that were not included in this update and the reasons for their exclusion are documented in Appendix D. The main reasons for exclusion were irrelevant comparator or irrelevant population.

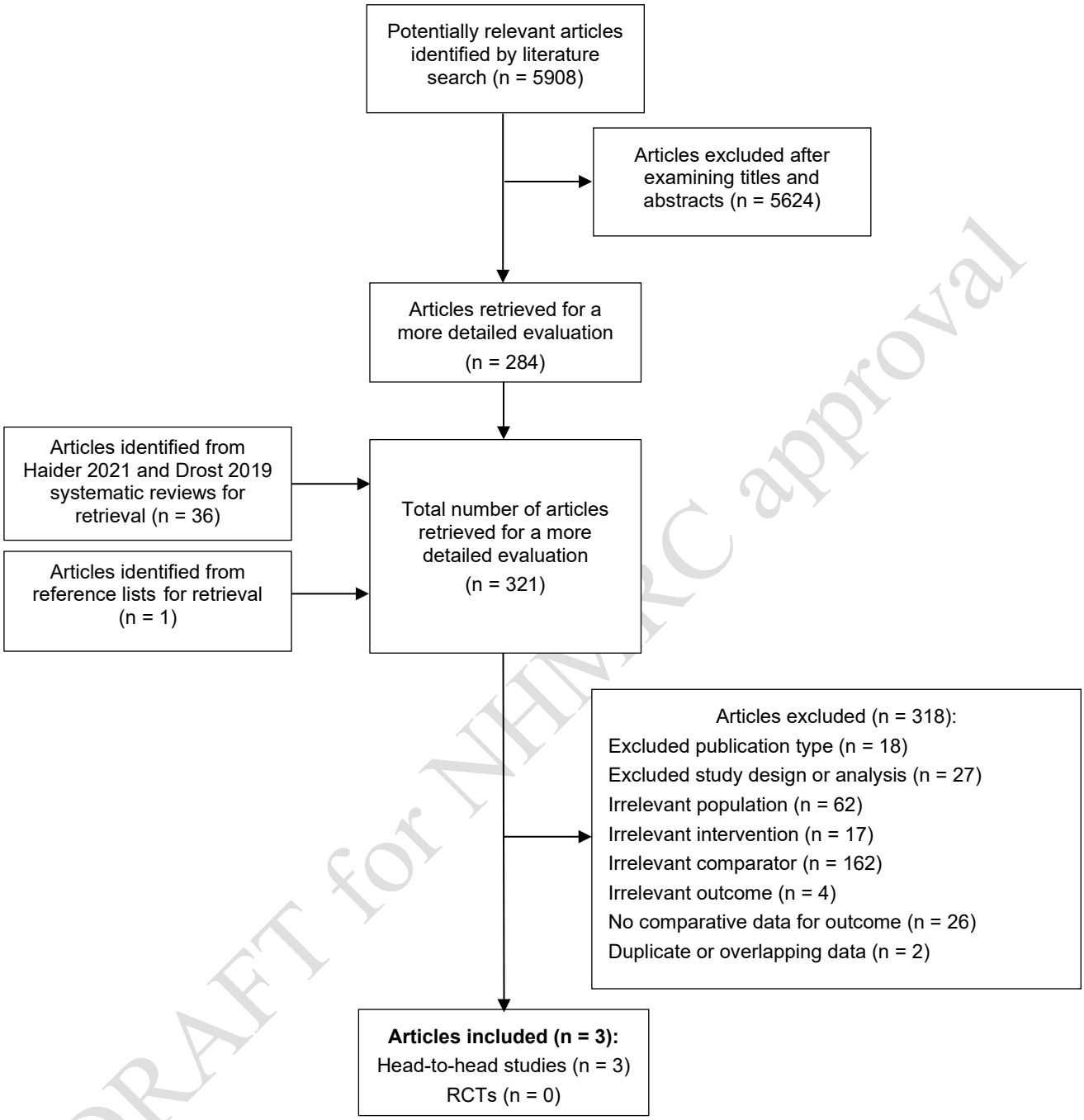

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

2.3 Characteristics of included studies

Table 3. *Study characteristics of included head-to-head (paired) studies reporting detection of clinically significant prostate cancer by multiparametric MRI-targeted biopsy alone compared to combined systematic and MRI-targeted biopsy in biopsy-naïve men with mpMRI score 3 lesion.*

Study	*Setting and study period*	*Population*	*mpMRI*	*mpMRI-Targeted biopsy (TB)*	*Systematic biopsy (SB)*	*Combined biopsy (SB + TB)*	*Outcomes of interest*
Hansen 2018 Germany, United Kingdom, Australia Prospective	Three tertiary centres 2012-2016	Men aged <80 years with mpMRI score 3 lesion (PIRADS v1 pre-2015 or v2 2015 onwards) undergoing TB + SB N = 137 Biopsy naïve: 100% Age mean: NR PSA level mean: NR	Read by radiologists with team-based peer-review of images in equivocal cases and ongoing histological feedback on >150 MRI/year	Transperineal TRUS-Fusion TB (2 centres) or Cognitive TB (1 centre) Prior to SB ≥2 cores per lesion Median (IQR) 4 (2-5) cores per patient^	Transperineal Ginsburg protocol: 3-4 cores per each of 6 prostate sectors using 5mm brachytherapy grid	Median (IQR) 26 (24-28) cores per patient^	ISUP Grade ≥ 2 *Reported as Gleason Score*
Mortezavi 2018 Switzerland Retrospective	Single tertiary centre 2014-2016	Men with mpMRI score 3 lesion (5-point Likert scale) undergoing TB + SB N = 36 Biopsy naïve: 100% Age mean: NR PSA level mean: NR	Read by board certified radiologists (number and experience NR)	Transperineal TRUS-Fusion TB After SB 2-4 cores per lesion Median (IQR) 3 (2-4) cores per patient^	Transperineal template saturation biopsy according to Barzell zones (20 zones) Median (range) 40 (30-55) cores per patient^	Total cores per patient NR	ISUP Grade ≥ 2 *Reported as Gleason Score*
Bonekamp 2019 Germany Retrospective	Single research centre 2015-2016	Men with mpMRI score 3 lesion (PIRADS v2) undergoing TB + SB N = 38 Biopsy naïve: 100% Age mean: NR PSA level mean: NR	Read by 8 board certified radiologists; 98% read by 7 radiologists with > 3 years of experience in prostate MR image interpretation	Transperineal TRUS-Fusion TB Prior to SB Median (range) 4 (3-5) cores per lesion^	Transperineal biopsy (Ginsburg protocol) Median (range) 23 (20-26) cores per patient^	Median (range) 29 (24-33) cores per patient^	ISUP Grade ≥ 2 *Reported as Gleason Score* ISUP Grade ≥ 3 results unable to be extracted

ISUP = International Society of Urological Pathology; IQR = interquartile range; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; N = number; NR = not reported; PIRADS = Prostate Imaging Reporting and Data System; SB = systematic biopsy; TB = targeted biopsy; TRUS = transrectal ultrasound-guided; v = version
^ Median biopsy cores for overall population with mpMRI score 3-5

2.4 Results by outcome of interest

Clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) – results are shown in Table 4, and Figures 2 and 3

ISUP grade ≥ 3 prostate cancer – no results

ISUP grade 1 prostate cancer – no results

*1. Results for the detection of **clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer)***

Table 4. *Detection of **clinically significant prostate cancer** (ISUP grade ≥ 2 prostate cancer) by MRI-targeted biopsy alone compared to combined systematic and MRI-targeted biopsy in biopsy-naïve men with mpMRI score 3 lesion*

Study	***N***	***csPrCa detected (n)***		***csPrCa undetected if perform TB only***	***Relative sensitivity of TB*** (95% CI)	***csPrCa prevalence***	***Undetected csPrCa per 1000 for a prevalence of 30%*** (95%CI)
		TB	***SB + TB***				
Hansen 2018	137	29	41	12	0.707 (0.56, 0.84)	29.9%	87 (48-132)
Mortezavi 2018	36	7	11	4	0.636 (0.33, 0.90)	30.6%	108 (30-201)
Bonekamp 2019	38	3*	8*	5*	0.375 (0.07, 0.74)	21.1%	188 (78-279)

CI = confidence interval; csPrCa = clinically significant prostate cancer; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; N = number; SB = systematic biopsy; TB = targeted biopsy
** Results reported for cancers detected in the MRI-positive area rather than for targeted biopsies*

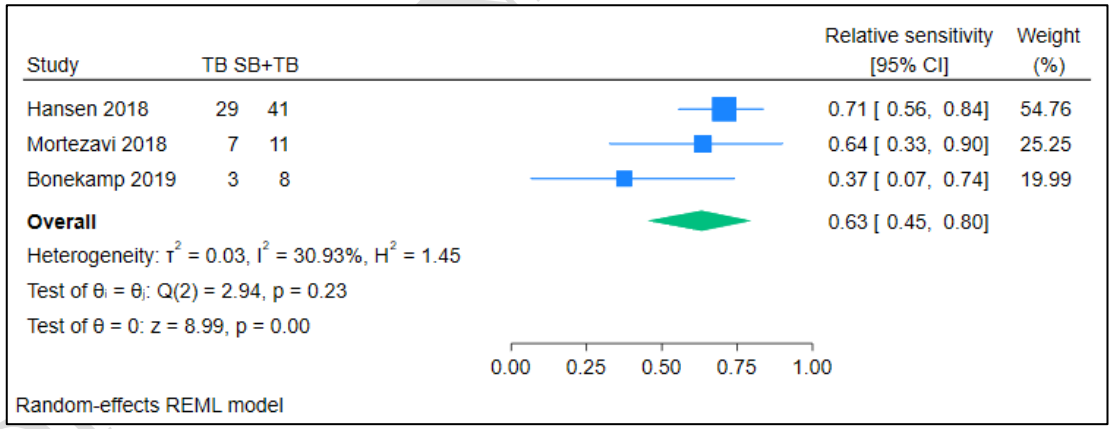

Figure 2. *Forest plot of the sensitivity of MRI-targeted biopsy (TB) relative to combined systematic and MRI-targeted biopsy (SB + TB) for the detection of clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) in biopsy-naïve men with mpMRI score 3 lesion. REML = restricted maximum likelihood.*

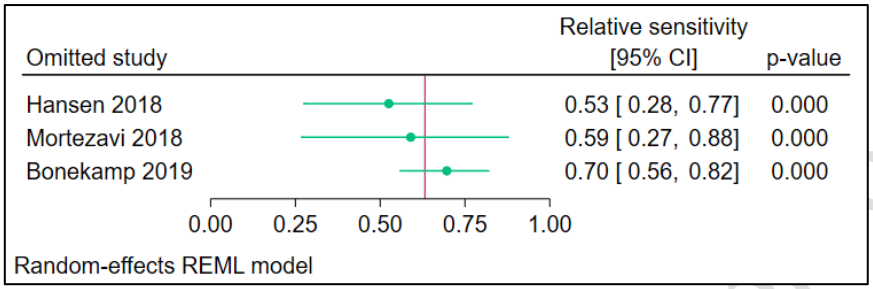

Figure 3. *Forest plot of sensitivity analysis results using the leave-one-out method to show impact of each study on pooled sensitivity of MRI-targeted biopsy relative to combined systematic and MRI-targeted biopsy for the detection of clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) in biopsy-naïve men with mpMRI score 3 lesion. REML = restricted maximum likelihood.*

2.5 Risk of bias

The results of the risk of bias assessments for the included studies are shown in Table 5.

Table 5. *Risk of bias assessments for included head-to-head (paired) studies using a modified version of the Quality of Diagnostic Accuracy Studies-2 (QUADAS-2) risk of bias assessment tool (Whiting 2011).*

Study	Outcome	Risk of bias			Overall
		Patient selection	Index tests	Flow	
Hansen 2018	ISUP grade ≥2 prostate cancer	Low	Unclear	Low	Unclear
Mortezavi 2018	ISUP grade ≥2 prostate cancer	Low	Unclear	Low	Unclear
Bonekamp 2019	ISUP grade ≥2 prostate cancer	Low	Unclear	Low	Unclear

ISUP = International Society of Urological Pathology

3. GRADE assessment of the certainty of the evidence

Detection of clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) – Table 6

Detection of ISUP grade ≥ 3 prostate cancer – no results

Detection of ISUP grade 1 prostate cancer – no results

Table 6. *GRADE assessment of the certainty of the evidence for the sensitivity of MRI-targeted biopsy relative to combined systematic and MRI-targeted biopsy to detect ISUP Grade ≥ 2 prostate cancer in biopsy-naïve men with mpMRI score 3 lesion*

GRADE domain	*Rating*	*Reason for rating*	*Certainty of evidence*
Risk of bias	No serious concerns	All 3 studies reported this outcome and none of the sources of bias were considered to be at high risk of bias. The overall risk of bias was unclear due to unclear blinding of the index test, but this was not considered likely to have caused major distortions to the results for this PICO.	*HIGH*
Indirectness	No serious concerns	All 3 studies performed a systematic biopsy consisting of ≥20 cores for all men, which is recommended as the standard of care in the Australian setting. Two of the three studies reported results for targeted biopsy alone whereas the third study reported results for biopsies within the MRI-positive area rather than targeted biopsies (Bonekamp 2019). Only one study used PIRADS v2 exclusively; one study used primarily PIRADS v1 and the other study used a Likert scale	
Imprecision	No serious concerns with respect to whether the number of clinically significant cancers undetected were clinically important or unimportant	If prevalence of ISUP Grade ≥ 2 prostate cancer is 30%, in a population of 1000 biopsy-naïve men with mpMRI score 3 lesion, 111 (60-165) ISUP Grade ≥ 2 prostate cancers would not be detected if perform MRI-targeted biopsy only. For ISUP Grade ≥ 2 prostate cancer not detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI crossed one threshold, but it did not cross the threshold for a clinically **unimportant** difference. Sensitivity analysis excluding Bonekamp 2019 (study reporting the lowest relative sensitivity): If prevalence of ISUP Grade ≥ 2 prostate cancer is 30%, in a population of 1000 biopsy-naïve men with mpMRI score 3 lesion, 90 (54-132) ISUP Grade ≥ 2 prostate cancers would not be detected if perform MRI-targeted biopsy only. For ISUP Grade ≥ 2 prostate cancer not detected using a MCID of 50/1000 and thresholds for moderate and large effects of 100/1000 and 200/1000 the 95%CI crossed one threshold, but it did not cross the threshold for a clinically **unimportant** difference.	
Inconsistency	No serious concerns	There were > 10 percentage points between highest and lowest point estimates for relative sensitivity (Hansen 2018 0.71, Bonekamp 2019 0.37). CIs overlapped and heterogeneity was not observed when results of the 3 studies were pooled (I^2 = 30.9%, p = 0.23). The lower relative sensitivity reported by Bonekamp 2019 could be explained by results being reported for cancers detected in the MRI positive area, rather than for targeted biopsies, however such an approach would potentially result in larger estimates of the relative sensitivity for targeted biopsies. Differences in relative sensitivity may also be explained by differences in the MRI assessment tools used in each study i.e. PIRADS v2, PIRADS v1 and a Likert scale, the experience of radiologists reading the MRI images and the order in which biopsies were taken.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 studies. All 3 studies either reported no direct funding by industry and/or declared no conflicts of interest.	

CI = confidence interval; ISUP = International Society of Urological Pathology; MCID = minimal clinically important difference; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging

4. Summary of findings

Table 7. *Summary of findings for MRI-targeted biopsy alone compared to combined systematic and MRI-targeted biopsy in biopsy-naïve men with mpMRI score 3 lesion*

Outcome ***(MCID)***	***Studies (participants)***	***Summary relative sensitivity***	***Outcome prevalence***	***Numbers undetected per 1000 if perform MRI-targeted biopsy only*** *(95% CI)*	***Certainty of the evidence (GRADE)***	***Plain text summary***
Clinically significant prostate cancer (ISUP grade ≥ 2 prostate cancer) (50/1000)	3 (211)	0.63 (0.45, 0.80)	30%	111 (60, 165)	High	For biopsy-naïve men with a mpMRI score 3 lesion **a clinically important** (moderate)^ number of clinically significant cancers will not be detected if a ≥ 20 core systematic biopsy is not undertaken in addition to a targeted biopsy
	*Sensitivity analysis** 2 (173)	0.70 (0.56, 0.82)	30%	90 (54, 132)		
ISUP grade ≥ 3 prostate cancer (35/1000)	0	No results found				No evidence found
ISUP grade 1 prostate cancer (100/1000)	0	No results found				No evidence found

CI = confidence interval; ISUP = International Society of Urological Pathology grade; MCID = minimal clinically important difference; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging

** Excluded study reporting the lowest relative sensitivity*

^ Using thresholds of 50, 100 and 200 undetected ISUP Grade ≥ 2 prostate cancer/1000 for small (MCID), moderate and large effects

5. Ongoing clinical trials

One potentially relevant ongoing trial protocol was identified by searches of clinical trial registries or literature searches.

Table 8. *Summary of potentially relevant ongoing randomised controlled trial comparing biopsy protocols with lower numbers of biopsy and include a targeted biopsy with a systematic biopsy of ≥ 20 cores with or without MRI-targeted biopsy*

Study ID Publications	Study name, location and study design	Start date	Planned completion date	Population	Intervention	Comparator	Outcomes
NCT04685928	Extended Systematic Versus Mri-Assisted pRostate Transperineal Biopsy (SMART) trial Hong Kong RCT – 2 arms	2021 Recruiting	2025	Biopsy-naïve men aged ≥18 years with clinical suspicion of prostate cancer based on elevated PSA (4-20 ng/ml) +/- abnormal DRE	mpMRI If PIRADS score 3-5, transperineal MRI-targeted biopsy (3-4 cores) + 12-core systematic biopsy (sparing MRI targets) If PIRADS score 1-2, no biopsy	No mpMRI Transperineal 24-core systematic biopsy for all men	*Primary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection *Secondary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection of MRI-targeted biopsy only vs systematic biopsy only Clinically insignificant prostate cancer (ISUP Grade 1) detection Biopsies avoided among mpMRI negative men Maximum cancer core length Adverse events at 30 days post biopsy Health-related quality of life Cost per diagnosis of cancer

DRE = digital rectal examination; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PIRADS = Prostate Image-Reporting and Data System; RCT = randomised controlled trial

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Hansen NL, Barrett T, Kesch C, et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer. BJU Int. 2018 Jul;122(1):40-49.

Mortezavi A, Märzendorfer O, Donati OF, et al. Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging and Fusion Guided Targeted Biopsy Evaluated by Transperineal Template Saturation Prostate Biopsy for the Detection and Characterization of Prostate Cancer. J Urol. 2018 Aug;200(2):309-318.

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Whiting PF, Rutjes AW, Westwood ME, QUADAS-2 Group, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36.

APPENDICES

A.1 Search strategies for systematic reviews published 2010 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2010 -Current"
20	(Systematic* adj3 review*).tw.
21	(meta-analys* or meta analys*).tw.
22	20 or 21
23	19 and 22
24	remove duplicates from 23

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2010 and Jan 2025, in Cochrane Reviews (Word variations have been searched)

A.2a Search strategies for primary randomised controlled trials published 2018 onwards

Databases: Medline, Embase and Cochrane Central Register of Controlled Trials databases (via Ovid platform)

#	Searches
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
21	Randomized Controlled Trial/
22	exp Randomized Controlled Trials as Topic/
23	"Randomized Controlled Trial (topic)"/
24	Controlled Clinical Trial/
25	exp Controlled Clinical Trials as Topic/
26	"Controlled Clinical Trial (topic)"/
27	Randomization/
28	Random Allocation/
29	Double-Blind Method/
30	Double Blind Procedure/
31	Double-Blind Studies/
32	Single-Blind Method/
33	Single Blind Procedure/
34	Single-Blind Studies/
35	Placebos/
36	Placebo/
37	Control Groups/
38	Control Group/
39	(random* or sham or placebo*).ti,ab,hw,kf.
40	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
41	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
42	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
43	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
44	allocated.ti,ab,hw.
45	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
46	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
47	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
48	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
49	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
50	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
51	or/20-50
52	19 and 51
53	remove duplicates from 52

A.2b Search strategies for primary studies published 2018 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	from 19 keep 1-6000
21	remove duplicates from 20
22	from 19 keep 6001-7458
23	remove duplicates from 22
24	21 or 23
25	remove duplicates from 24

Appendix B: GRADE assessment of the certainty of the evidence

Ratings	*Definitions*
⊕⊕⊕⊕ High certainty	The panel is very confident that the true effect lies close to that of the estimate of the effect
⊕⊕⊕◯ Moderate certainty	The panel is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ Low certainty	The panel's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕◯◯◯ Very low certainty	The panel has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reported based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Systematic reviews of the evidence were not accessible.

Appendix D: Excluded Studies

Article	*DOI*	*Reason for exclusion*
Articles from primary studies search for randomised controlled trials		
Ahlberg 2019	https://dx.doi.org/10.1136/bmjopen-2018-027860	Irrelevant population
Alberts 2019	https://dx.doi.org/10.1016/j.eururo.2018.07.031	Excluded study design
Alkema 2022	https://dx.doi.org/10.1016/j.euros.2022.08.005	Excluded study design
Alterbeck 2024	https://dx.doi.org/10.1111/bju.16143	Excluded study design
Amin 2020	https://dx.doi.org/10.1111/bju.14999	Excluded study design
Arsov 2022	https://dx.doi.org/10.1002/ijc.33940	Irrelevant population
Auvinen 2024	https://dx.doi.org/10.1001/jama.2024.3841	Irrelevant population
Baccaglini 2021	https://dx.doi.org/10.1016/j.clgc.2020.06.008	Excluded study design
Bates 2023	https://doi.org/10.1016/S0302-2838(23)00144-6	Excluded publication type
Bjornebo 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.7131	Irrelevant population
Boschheidgen 2024	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Excluded study design
Bratt 2019	https://dx.doi.org/10.1016/j.eururo.2019.02.035	Irrelevant population
Bryant 2023	https://dx.doi.org/10.1111/bju.15978	Irrelevant comparator
Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Excluded study design
Checcucci 2022	https://doi.org/10.1016/S2666-1683(22)01175-2	Excluded publication type
Checcucci 2023	https://doi.org/10.21873/anticanres.16021	Excluded publication type
Checcucci 2024	https://doi.org/10.1016/S0302-2838(22)00538-3	Excluded publication type
Checcucci 2022	https://doi.org/10.1097/JU.0000000000002555.11	Excluded publication type
Chen 2018	https://dx.doi.org/10.1016/j.ajur.2017.07.001	Excluded study design
ChiCTR2000036915 2020	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000036915	Excluded publication type
Choi 2019	https://dx.doi.org/10.1016/j.clgc.2018.09.007	Excluded study design
Dadpour 2023	https://pubmed.ncbi.nlm.nih.gov/37645612/	Irrelevant population
DRKS00032422 2023	https://drks.de/search/en/trial/DRKS00032422	Excluded publication type
Eineluoto 2018	https://dx.doi.org/10.1016/j.euo.2018.02.005	Excluded study design
Eklund 2021	https://dx.doi.org/10.1056/NEJMoa2100852	Irrelevant comparator
Elwenspoek 2019	https://dx.doi.org/10.1001/jamanetworkopen.2019.8427	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Excluded study design
Ettala 2022	https://dx.doi.org/10.1136/bmjopen-2021-053118	Irrelevant intervention
Exterkate 2020	https://dx.doi.org/10.1016/j.euo.2019.06.005	Irrelevant population
Exterkate 2023	https://dx.doi.org/10.1111/bju.15876	Irrelevant population
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	Irrelevant comparator
Ghai 2024	https://dx.doi.org/10.1148/radiol.231948	Irrelevant population
Guo 2024	https://dx.doi.org/10.1186/s13244-024-01699-4	Excluded study design
Hamid 2019	https://dx.doi.org/10.1016/j.eururo.2018.08.007	Excluded study design

He 2021	https://dx.doi.org/10.1136/bmjopen-2020-041427	Excluded publication type
Hu 2020	https://dx.doi.org/10.1007/s00261-019-02370-z	Irrelevant comparator
Hugosson 2022	https://dx.doi.org/10.1056/NEJMoa2209454	Irrelevant comparator
Hugosson 2019	https://doi.org/10.1016/S1569-9056(19)31108-X	Excluded publication type
Israel 2022	https://dx.doi.org/10.1111/bju.15562	Excluded study design
ISRCTN60263108 2022	https://www.isrctn.com/ISRCTN60263108	Excluded publication type
Izadpanahi 2021	https://dx.doi.org/10.1038/s41391-021-00366-9	Irrelevant comparator
Jahnen 2024	https://doi.org/10.1016/S0302-2838(24)00876-5	Excluded publication type
Jahnen 2023	https://doi.org/10.1016/S0302-2838(23)00355-X	Excluded publication type
Jiang 2024	https://dx.doi.org/10.1016/j.euo.2023.12.002	Irrelevant comparator
Kasivisvanathan 2018	https://dx.doi.org/10.1056/NEJMoa1801993	Irrelevant comparator
Kasivisvanathan 2019	https://dx.doi.org/10.1016/j.eururo.2019.04.043	Irrelevant comparator
Kasivisvanathan 2022	https://dx.doi.org/10.1371/journal.pone.0263345	Irrelevant comparator
Kelly 2023	https://dx.doi.org/10.1016/j.euros.2023.05.002	Excluded study design
Klotz 2020	https://dx.doi.org/10.1016/j.eururo.2019.10.007	Irrelevant population
Klotz 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7589	Irrelevant comparator
Klotz 2022	https://dx.doi.org/10.1016/j.cct.2021.106618	Irrelevant intervention
Klotz 2024	https://dx.doi.org/10.1016/j.euo.2023.09.013	Irrelevant population
Kohestani 2021	https://dx.doi.org/10.1080/21681805.2021.1881612	Irrelevant population
Kruger-Stokke 2021	https://dx.doi.org/10.3389/fonc.2021.745657	Irrelevant comparator
Liu 2024	https://dx.doi.org/10.1136/bmjopen-2023-080593	Excluded study design
Luzzago 2021	https://dx.doi.org/10.1038/s41391-020-00290-4	Excluded study design
Mian 2024	https://dx.doi.org/10.1097/JU.0000000000003979	Excluded study design
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	Excluded study design
Morote 2024	https://dx.doi.org/10.3390/cancers16132306	Excluded study design
NCT03572946 2018	https://clinicaltrials.gov/study/NCT03572946	Excluded publication type
NCT04993508 2021	https://clinicaltrials.gov/study/NCT04993508	Excluded publication type
NCT04953351 2021	https://clinicaltrials.gov/study/NCT04953351	Excluded publication type
NCT06303622 2024	https://clinicaltrials.gov/study/NCT06303622	Excluded publication type
NCT03632655 2018	https://clinicaltrials.gov/study/NCT03632655	Excluded publication type
NICE 2019	https://www.ncbi.nlm.nih.gov/books/NBK576979/	Excluded study design
Nordstrom 2021	https://dx.doi.org/10.1016/S1470-2045%2821%2900348-X	Irrelevant population
Nordstrom 2024	https://dx.doi.org/10.1001/jamanetworkopen.2023.54577	Irrelevant population
Panebianco 2018	https://dx.doi.org/10.1016/j.euo.2018.03.008	Irrelevant outcome
Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Porpiglia 2023	https://dx.doi.org/10.23736/S2724-6051.22.05189-8	Irrelevant comparator
Porreca 2020	https://dx.doi.org/10.1097/MD.0000000000022059	Irrelevant population
Prince 2021	https://dx.doi.org/10.2214/AJR.20.25207	Excluded study design
Rabah 2021	https://dx.doi.org/10.15537/smj.2021.42.6.20200771	Irrelevant comparator
Rai 2021	https://dx.doi.org/10.1016/j.euo.2020.12.012	Irrelevant comparator
Rakauskas 2023	https://dx.doi.org/10.1371/journal.pone.0280262	Excluded study design
Russo 2021	https://dx.doi.org/10.1016/j.euo.2021.03.007	Irrelevant comparator
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	Irrelevant population
Schiavina 2021	https://dx.doi.org/10.1016/j.urolonc.2020.10.018	Irrelevant population

Szewczyk-Bieda 2019	https://dx.doi.org/10.1186/s13063-019-3746-0	Irrelevant comparator
Wagensveld 2021	https://doi.org/10.1016/S0302-2838(21)01279-3	Excluded publication type
Wang 2023	https://dx.doi.org/10.1007/s00345-022-04086-0	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.eururo.2018.11.040	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.euo.2019.08.007	Irrelevant population
Wei 2023	https://dx.doi.org/10.1148/radiol.221428	Irrelevant population
Woo 2019	https://dx.doi.org/10.1016/j.euo.2019.05.004	Irrelevant comparator
Yang 2024	https://dx.doi.org/10.1016/j.acra.2024.08.027	Excluded study design
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Excluded study design
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant comparator
Zhang 2022	https://dx.doi.org/10.3389/fsurg.2022.1058288	Irrelevant comparator
Zhu 2018	https://dx.doi.org/10.7150/jca.24690	Irrelevant comparator
Articles from primary studies search and citation search for head-to-head studies		
Agrotis 2023	https://dx.doi.org/10.1002/jcu.23497	Irrelevant comparator
Ahdoot 2020	https://dx.doi.org/10.1056/NEJMoa1910038	Irrelevant comparator
Ahmed 2017	https://doi.org/10.1016/S0140-6736(16)32401-1	Irrelevant intervention
Alqahtani 2021	https://dx.doi.org/10.3390/cancers14010001	Irrelevant comparator
Alqahtani 2022	https://dx.doi.org/10.3390/cancers14010001	Irrelevant comparator
An 2024	https://dx.doi.org/10.1007/s00345-024-04947-w	Irrelevant comparator
Andras 2019	https://dx.doi.org/10.11152/mu-1705	Irrelevant comparator
Araujo 2023	https://dx.doi.org/10.4081/aiua.2023.11830	Irrelevant comparator
Avolio 2023	https://dx.doi.org/10.1007/s00345-023-04480-2	Irrelevant comparator
Bangash 2021	https://dx.doi.org/10.53350/pjmhs2115102625	Irrelevant population
Barrett 2019	https://dx.doi.org/10.1016/j.crad.2019.06.004	Irrelevant comparator
Barrett 2016	https://doi.org/10.1007/s00345-015-1650-0	Irrelevant population
Barth 2021	https://dx.doi.org/10.1016/j.ejro.2021.100332	Irrelevant intervention
Bass 2018	https://dx.doi.org/10.1136/bmjopen-2018-024941	Irrelevant comparator
Bastian-Jordan 2018	https://dx.doi.org/10.1111/1754-9485.12678	Irrelevant comparator
Bhat 2020	https://dx.doi.org/10.1080/13685538.2019.1641796	Irrelevant population
Boeve 2023	https://dx.doi.org/10.1111/bju.16041	No comparative data for outcome
Borghesi 2021	https://dx.doi.org/10.23736/S2724-6051.20.03758-3	Irrelevant comparator
Bosaily 2020	https://dx.doi.org/10.1016/j.eururo.2020.03.002	Irrelevant intervention
Boschheidgen 2023	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Irrelevant comparator
Bourgeno 2024	https://dx.doi.org/10.1016/j.euo.2024.01.007	Irrelevant comparator
Briggs 2021	https://dx.doi.org/10.1016/j.urology.2021.04.040	Irrelevant population
BrizmohunAppayya 2018	https://dx.doi.org/10.1259/bjr.20170645	Irrelevant population
Camacho 2023	https://doi.org/10.1002/bco2.231	Irrelevant comparator
Cetin 2023	https://dx.doi.org/10.18621/eurj.1198992	Irrelevant population
Chaloupka 2023	https://dx.doi.org/10.1111/bju.16248	Irrelevant comparator
Chandra Engel 2024	https://doi.org/10.1016/j.euo.2024.10.002	Irrelevant comparator
Chau 2018	https://dx.doi.org/10.1016/j.ijso.2018.01.002	Irrelevant population
Chau 2024	https://dx.doi.org/10.1007/s11845-024-03637-1	Irrelevant comparator
Checcucci 2020	https://dx.doi.org/10.23736/S0393-2249.20.03958-2	Irrelevant comparator

Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Irrelevant comparator
Cheng 2021	https://dx.doi.org/10.3389/fonc.2021.643051	Irrelevant comparator
Cheng 2022	https://dx.doi.org/10.1080/08941939.2020.1825884	Irrelevant comparator
Choomark 2023	https://dx.doi.org/10.33192/smj.v75i11.265361	Irrelevant comparator
Connor 2020	https://dx.doi.org/10.1097/JU.0000000000001184	Irrelevant comparator
D'Agostino 2019	https://dx.doi.org/10.4081/aiua.2019.2.87	Irrelevant comparator
D'Agostino 2020	https://dx.doi.org/10.4081/aiua.2019.4.211	Irrelevant comparator
Dahl 2022	https://dx.doi.org/10.1016/j.urolonc.2022.07.011	Irrelevant population
Dahl 2024	https://dx.doi.org/10.1016/j.urolonc.2023.11.004	Irrelevant population
Del Monte 2018	https://dx.doi.org/10.1007/s11547-017-0825-8	Irrelevant comparator
Dell'Oglio 2020	https://dx.doi.org/10.1016/j.euo.2019.03.002	Irrelevant comparator
Demirtas 2019	https://dx.doi.org/10.7759/cureus.6160	Irrelevant comparator
Deniffel 2022	https://dx.doi.org/10.1007/s00330-022-08822-3	Irrelevant population
Dhir 2023	https://dx.doi.org/10.1016/j.urology.2023.04.017	Irrelevant comparator
Diez 2024	https://doi.org/10.1007/s00345-024-05233-5	No comparative data for outcome
Donato 2020	https://dx.doi.org/10.1007/s00345-019-02774-y	Irrelevant comparator
Dragoescu 2023	https://dx.doi.org/10.3390/diagnostics13081373	Irrelevant comparator
Droghetti 2023	https://dx.doi.org/10.1007/s00345-022-04229-3	Irrelevant comparator
Eldred-Evans 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7456	Irrelevant comparator
Elfatairy 2019	https://dx.doi.org/10.1148/rycan.2019190016	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.2967/jnumed.121.263448	Excluded study design
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Irrelevant intervention
Emmett 2023	https://dx.doi.org/10.2967/jnumed.123.266164	Irrelevant intervention
Falagario 2021	https://dx.doi.org/10.1111/iju.14385	Irrelevant comparator
Fleville 2024	https://dx.doi.org/10.1097/JU.0000000000004226	Irrelevant comparator
Freifeld 2019	https://dx.doi.org/10.1016/j.urolonc.2018.10.009	Irrelevant comparator
Fulco 2021	https://dx.doi.org/10.3390/cancers13194833	Irrelevant comparator
Furrer 2022	https://dx.doi.org/10.1111/ans.17713	Irrelevant comparator
Gavin 2020	https://dx.doi.org/10.1016/j.euros.2020.07.001	Irrelevant population
Gayet 2020	https://dx.doi.org/10.1155/2020/4626781	Irrelevant comparator
Gomez-Gomez 2021	https://dx.doi.org/10.3390/diagnostics11081335	Irrelevant comparator
Gorin 2020	https://dx.doi.org/10.1007/s00345-019-02992-4	Irrelevant comparator
Gortz 2022	https://dx.doi.org/10.3390/cancers14040886	Irrelevant population
Grey 2022	https://dx.doi.org/10.1016/S1470-2045(22)00016-X	Irrelevant comparator
Gross 2020	https://dx.doi.org/10.1097/JU.0000000000000534	Irrelevant comparator
Gunzel 2022	https://dx.doi.org/10.1007/s11255-022-03309-y	Irrelevant comparator
Hagens 2022	https://dx.doi.org/10.1016/j.euros.2022.07.006	Irrelevant comparator
Hagens 2022	https://dx.doi.org/10.1016/j.euros.2022.04.001	Irrelevant population
Hansen 2020	https://dx.doi.org/10.1111/bju.14865	Irrelevant population
Henning 2021	https://dx.doi.org/10.1016/j.urolonc.2020.11.018	Irrelevant comparator
Hepp 2022	https://dx.doi.org/10.1007/s00345-022-03991-8	Irrelevant population
Ho 2023	https://dx.doi.org/10.1016/j.urolonc.2023.11.005	Irrelevant population
Hofbauer 2022	https://dx.doi.org/10.1111/bju.15635	Irrelevant population

Hogan 2022	https://dx.doi.org/10.1177/20514158221084820	No comparative data for outcome
Hogan 2024	https://dx.doi.org/10.1177/20514158221084820	Duplicate
Hou 2022	https://dx.doi.org/10.1038/s41391-021-00489-z	Irrelevant comparator
Hsi 2023	https://dx.doi.org/10.1002/bco2.184	No comparative data for outcome
Hsieh 2022	https://dx.doi.org/10.31083/j.jomh1806127	Irrelevant population
Huang 2022	https://dx.doi.org/10.2147/CMAR.S350701	Irrelevant comparator
Hubbard 2021	https://pubmed.ncbi.nlm.nih.gov/34786148/	Irrelevant population
Hung 2024	https://dx.doi.org/10.1016/j.urology.2023.11.039	Irrelevant comparator
Jahnen 2023	https://dx.doi.org/10.1007/s00345-023-04564-z	Irrelevant comparator
Kachanov 2022	https://dx.doi.org/10.1097/JU.0000000000002248	Irrelevant comparator
Kalapara 2022	https://dx.doi.org/10.1016/j.euo.2021.02.006	No comparative data for outcome
Kam 2018	https://dx.doi.org/10.1016/j.prnil.2017.10.003	Irrelevant population
Kasivisvanathan 2024	https://doi.org/10.1016/j.eururo.2024.08.022	Irrelevant comparator
Kato 2021	https://dx.doi.org/10.3390/curroncol28020123	Irrelevant comparator
Kaufmann 2022	https://dx.doi.org/10.1002/pros.24286	Irrelevant population
Khoo 2021	https://dx.doi.org/10.1097/JU.0000000000001476	Irrelevant population
Kim 2021	https://dx.doi.org/10.1007/s00330-020-07167-z	Irrelevant comparator
Kim 2022	https://dx.doi.org/10.1097/JU.0000000000002168	No comparative data for outcome
Kong 2023	https://dx.doi.org/10.1177/20514158211065946	No comparative data for outcome
Kortenbach 2021	https://dx.doi.org/10.1016/j.heliyon.2021.e08325	No comparative data for outcome
Krausewitz 2023	https://dx.doi.org/10.1007/s00345-022-04230-w	Irrelevant comparator
Kuhlmann 2022	https://dx.doi.org/10.1016/j.urolonc.2021.12.016	Irrelevant comparator
Kurokawa 2024	https://dx.doi.org/10.21873/anticanres.16858	Irrelevant comparator
Kwon 2023	https://dx.doi.org/10.1007/s11255-023-03674-2	No comparative data for outcome
Labra 2020	https://dx.doi.org/10.1007/s00261-020-02481-y	Irrelevant comparator
Lahoud 2021	https://dx.doi.org/10.1111/ans.16524	No comparative data for outcome
Lee 2020	https://dx.doi.org/10.1111/bju.15118	No comparative data for outcome
Lee 2021	https://dx.doi.org/10.1016/j.urolonc.2021.02.027	Overlapping data
Lee 2022	https://dx.doi.org/10.1016/j.prnil.2021.08.003	Irrelevant population
Lee 2022	https://dx.doi.org/10.1038/s41391-021-00485-3	Irrelevant comparator
Leow 2023	https://dx.doi.org/10.4103/aja2021128	Irrelevant comparator
Liu 2020	https://dx.doi.org/10.1038/s41391-020-0260-0	Irrelevant comparator
Liu 2021	https://dx.doi.org/10.1259/bjr.20210312	Irrelevant comparator
Liu 2023	https://dx.doi.org/10.1002/jmri.28614	Irrelevant comparator
Lockhart 2022	https://dx.doi.org/10.1177/20514158221085081	No comparative data for outcome
Lombardo 2023	https://dx.doi.org/10.3390/life13081719	Irrelevant comparator
Lopez 2021	https://dx.doi.org/10.1111/bju.15337	No comparative data for outcome
Lovegrove 2020	https://dx.doi.org/10.1097/JU.0000000000000455	Irrelevant intervention
Lughezzani 2019	https://dx.doi.org/10.1016/j.euo.2018.10.001	Irrelevant comparator

Malewski 2023	https://dx.doi.org/10.3390/jcm12175612	Irrelevant comparator
Martin 2023	https://dx.doi.org/10.1007/s00345-023-04386-z	Irrelevant comparator
Mesko 2018	https://dx.doi.org/10.1097/COC.0000000000000308	Irrelevant comparator
Miah 2020	https://dx.doi.org/10.1007/s11701-019-00929-y	Irrelevant population
Mischinger 2018	https://dx.doi.org/10.1111/bju.14089	Irrelevant comparator
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	No comparative data for outcome
Morote 2023	https://dx.doi.org/10.3390/cancers15184543	Irrelevant comparator
Neale 2020	https://dx.doi.org/10.1111/bju.15092	Irrelevant population
Noujeim 2023	https://dx.doi.org/10.1038/s41391-022-00620-8	Irrelevant comparator
Novara 2023	https://dx.doi.org/10.1007/s00345-023-04382-3	Irrelevant outcome
Oderda 2024	https://dx.doi.org/10.3390/curroncol31070308	Irrelevant comparator
Oh 2020	https://dx.doi.org/10.4111/icu.2020.61.1.28	Irrelevant intervention
Olivetta 2024	https://dx.doi.org/10.3390/diagnostics14151643	Irrelevant comparator
Osses 2018	https://dx.doi.org/10.1159/000447216	Irrelevant comparator
Pang 2021	https://dx.doi.org/10.12998/wjcc.v9.i36.11183	Irrelevant comparator
Park 2020	https://dx.doi.org/10.3390/jcm9020530	Irrelevant comparator
Patel 2018	https://dx.doi.org/10.1016/j.euo.2018.03.009	Irrelevant comparator
Patel 2022	https://dx.doi.org/10.1097/JU.0000000000002120	Irrelevant comparator
Pepe 2022	https://dx.doi.org/10.21873/anticanres.15785	Irrelevant comparator
Petov 2023	https://dx.doi.org/10.1089/end.2022.0780	Irrelevant comparator
Phelps 2023	https://dx.doi.org/10.1007/s00261-022-03775-z	Irrelevant comparator
Ploussard 2019	https://dx.doi.org/10.1007/s00345-018-2399-z	Excluded study design
Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Pratihar 2023	https://dx.doi.org/10.4103/iju.iju_147_23	Irrelevant comparator
Rachubinski 2022	https://dx.doi.org/10.1097/JU.0000000000002921	Irrelevant population
Radtke 2019	https://dx.doi.org/10.1371/journal.pone.0221350	No comparative data for outcome
Rajendran 2024	https://dx.doi.org/10.1093/bjr/tqad027	No comparative data for outcome
Ruan 2023	https://dx.doi.org/10.1007/s00261-023-03894-1	Irrelevant comparator
Saba 2020	https://dx.doi.org/10.1097/JU.0000000000000622	No comparative data for outcome
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	No comparative data for outcome
Sanguedolce 2024	https://doi.org/10.1016/j.euo.2024.10.006	Irrelevant population
Sathianathen 2018	https://dx.doi.org/10.1038/s41391-018-0065-6	Irrelevant comparator
Sathianathen 2019	https://dx.doi.org/10.1111/bju.14617	Irrelevant comparator
Schelb 2019	https://dx.doi.org/10.1148/radiol.2019190938	Irrelevant outcome
Schmid 2023	https://dx.doi.org/10.1002/pros.24435	No comparative data for outcome
Senoglu 2022	https://dx.doi.org/10.4274/uob.galenos.2021.2021.4.1	Irrelevant comparator
Seref 2022	https://dx.doi.org/10.1002/pros.24255	Irrelevant population
Shefler 2024	https://dx.doi.org/10.1016/j.urolonc.2024.01.026	Irrelevant comparator
Siddiqui 2023	https://dx.doi.org/10.1038/s41391-023-00660-8	Irrelevant outcome
Sigle 2021	https://dx.doi.org/10.3390/cancers13102502	Irrelevant population
Sigle 2022	https://dx.doi.org/10.3390/cancers14215230	Irrelevant population

Sigle 2023	https://dx.doi.org/10.1016/j.euf.2023.01.020	Irrelevant population
Sivaraman 2022	https://dx.doi.org/10.4103/iju.iju_222_21	No comparative data for outcome
Song 2020	https://dx.doi.org/10.1097/JU.0000000000001302	Irrelevant comparator
Stabile 2021	https://dx.doi.org/10.1038/s41391-021-00371-y	Irrelevant comparator
Stavrinides 2023	https://dx.doi.org/10.1148/radiol.220762	Irrelevant population
Stevens 2023	https://dx.doi.org/10.1177/02841851231187135	Irrelevant intervention
Stone 2021	https://dx.doi.org/10.1002/bco2.111	Irrelevant intervention
Sugano 2020	https://dx.doi.org/10.1007/s11255-019-02354-4	Irrelevant comparator
Tae 2018	https://dx.doi.org/10.4111/icu.2018.59.6.363	Irrelevant comparator
Tay 2021	https://dx.doi.org/10.1002/bco2.99	Irrelevant intervention
Thangarasu 2021	https://dx.doi.org/10.2147/RRU.S300868	Irrelevant comparator
Thompson 2023	https://dx.doi.org/10.5152/tud.2023.22221	Irrelevant population
Tomioka 2023	https://dx.doi.org/10.3390/diagnostics13152608	Irrelevant comparator
Tschirdewahn 2021	https://dx.doi.org/10.1016/j.euf.2020.06.020	No comparative data for outcome
Tunc 2023	https://dx.doi.org/10.22037/uj.v20i.7610	Irrelevant comparator
Turkay 2020	https://dx.doi.org/10.1097/RUQ.0000000000000505	Irrelevant comparator
Velarde 2022	https://dx.doi.org/10.1007/s00261-021-03389-x	Irrelevant comparator
Wagaskar 2022	https://dx.doi.org/10.22037/uj.v18i.6852	No comparative data for outcome
Wang 2020	https://dx.doi.org/10.4103/aja.aja_83_19	Irrelevant comparator
Wang 2021	https://dx.doi.org/10.1186/s12894-021-00949-7	Irrelevant comparator
Washino 2018	https://dx.doi.org/10.1186/s12894-018-0361-4	Irrelevant comparator
Wei 2022	https://dx.doi.org/10.1007/s00261-022-03592-4	Irrelevant comparator
Weiser 2023	https://dx.doi.org/10.1002/jmri.28891	No comparative data for outcome
Wenzel 2021	https://dx.doi.org/10.3389/fsurg.2021.633196	Irrelevant intervention
Wong 2024	https://dx.doi.org/10.1016/j.euo.2024.01.002	No comparative data for outcome
Woo 2023	https://dx.doi.org/10.1016/j.euros.2022.11.012	Irrelevant comparator
Wu 2024	https://dx.doi.org/10.1038/s41391-023-00729-4	Irrelevant intervention
Yilmaz 2023	https://dx.doi.org/10.1148/radiol.221309	Irrelevant comparator
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Irrelevant population
Zambon 2024	https://dx.doi.org/10.1038/s41391-023-00770-3	Irrelevant comparator
Zattoni 2023	https://dx.doi.org/10.1007/s00345-023-04578-7	Irrelevant population
Zawaideh 2020	https://dx.doi.org/10.1259/bjr.20200298	Irrelevant comparator
Zhang 2018	https://dx.doi.org/10.1186/s12957-018-1367-9	Irrelevant intervention
Zhang 2019	https://dx.doi.org/10.1016/j.prnil.2018.10.001	Irrelevant comparator
Zhang 2020	https://dx.doi.org/10.1007/s10147-019-01524-9	Irrelevant population
Zhang 2020	https://dx.doi.org/10.21037/tau.2020.02.20	Irrelevant comparator
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant comparator
Zhang 2022	https://dx.doi.org/10.1186/s40644-022-00498-8	Irrelevant comparator
Zhu 2018	https://dx.doi.org/10.1097/MD.0000000000011962	Irrelevant comparator
Articles from Haider 2021 and Drost 2019 systematic reviews		
Alberts 2017	https://doi.org/10.1016/j.eururo.2017.06.019	Irrelevant comparator
Baco 2016	https://doi.org/10.1016/j.eururo.2015.03.041	Irrelevant comparator

Boesen 2018	https://doi.org/10.1001/jamanetworkopen.2018.0219	Irrelevant comparator
Borkowetz 2017	https://doi.org/10.1159/000477263	Irrelevant comparator
Borkowetz 2018	https://doi.org/10.1111/bju.14017	Irrelevant comparator
Castellucci 2017	https://doi.org/10.23736/s0393-2249.17.02845-4	Irrelevant comparator
Chen 2015	https://doi.org/10.3892%2Fetm.2014.2061	Irrelevant comparator
Cool 2016	https://doi.org/10.5489%2Fcuaj.3831	Irrelevant comparator
Delongchamps 2013	https://doi.org/10.1016/j.juro.2012.08.195	Irrelevant comparator
Distler 2017	https://doi.org/10.1016/j.juro.2017.03.130	Irrelevant population
Filson 2016	https://doi.org/10.1002/cncr.29874	Irrelevant comparator
Garcia Bennett 2017	https://doi.org/10.1016/j.diii.2017.06.010	Irrelevant comparator
Grey 2015	https://doi.org/10.1111/bju.12862	Irrelevant population
Gronberg 2018	https://doi.org/10.1016/j.eururo.2018.06.022	Irrelevant comparator
Jambor 2015	https://doi.org/10.1002/jmri.24682	Irrelevant comparator
Jambor 2017	https://doi.org/10.1002/jmri.25641	Irrelevant comparator
Kesch 2017	https://doi.org/10.1159/000458764	No comparative data for outcome
Kim 2017	https://doi.org/10.1016/j.urology.2016.08.074	Irrelevant comparator
Lee 2016	https://doi.org/10.3349/ymj.2016.57.3.565	Irrelevant comparator
Lee 2017	https://doi.org/10.3349%2Fymj.2017.58.5.994	Irrelevant comparator
Muthuveloe 2016	https://doi.org/10.5173/ceju.2016.675	Irrelevant population
Nafie 2014	https://pubmed.ncbi.nlm.nih.gov/28299763/	Irrelevant population
Okcelik 2016	https://doi.org/10.1590/s1677-5538.ibju.2015.0155	Irrelevant comparator
Panebianco 2015	https://doi.org/10.1016/j.urolonc.2014.09.013	Irrelevant comparator
Peltier 2015	https://doi.org/10.1155/2015/571708	Irrelevant comparator
Ploussard 2014	https://doi.org/10.1016/j.eururo.2012.05.049	Irrelevant population
Pokorny 2014	https://doi.org/10.1016/j.eururo.2014.03.002	Irrelevant comparator
Pressier 2019	https://doi.org/10.1016/j.euf.2019.06.015	Irrelevant comparator
Rouvière 2019	https://doi.org/10.1016/s1470-2045(18)30569-2	Irrelevant comparator
Sakar 2019	https://doi.org/10.1177/2051415819889552	Irrelevant comparator
Thompson 2016	https://doi.org/10.1016/j.juro.2015.10.140	No comparative data for outcome
Tonttilla 2016	https://doi.org/10.1016/j.eururo.2015.05.024	Irrelevant comparator
Van der Leest 2019	https://doi.org/10.1016/j.eururo.2018.11.023	Irrelevant comparator
Westoff 2019	https://doi.org/10.1016/j.urolonc.2019.07.004	Irrelevant comparator
Zalesky 2019	https://doi.org/10.5507/bp.2019.050	Irrelevant comparator
Zhang 2017	https://doi.org/10.1007/s11255-016-1484-8	Irrelevant comparator

3.14 Clinical question 9 – Prostate biopsy PICO 9B

Clinical question: *For biopsy naïve men with a PI-RADS 3 lesion on multiparametric MRI (mpMRI) are targeted biopsies alone acceptable/ reasonable/ adequate? (is a systematic biopsy necessary?)*

Introduction

This is the second of three systematic reviews which address Clinical question 9.

Systematic review report for PICO 9B: Comparison of prostate cancer detection by mpMRI targeted biopsy plus 12-core vs ≥ 20-core systematic biopsy

Authors

Chelsea Carle, Suzanne Hughes

PICO

This systematic review addresses the following PICO which is summarised in detail in Table 1.

PICO 9B: *For biopsy naïve men with a PI-RADS 3 lesion on mpMRI how do the rates of clinically significant and insignificant cancers detected using a targeted biopsy together with a 12-core systematic biopsy compare with those using a targeted biopsy together with a 20 or more-core systematic biopsy?*

Table 1. *PICO components*

Population	*Intervention*	*Comparator*	*Outcomes*	*Study design*
Biopsy naïve individuals with a PI-RADS 3 lesion on mpMRI	MRI-targeted biopsy + 12-core systematic biopsy	MRI-targeted biopsy + ≥ 20 core systematic biopsy	Detection of • ≥ ISUP grade 2 prostate cancer • ISUP grade 1 prostate cancer • ≥ ISUP grade 3 prostate cancer	Randomized controlled trial Or Fully paired comparison

ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PI-RADS = Prostate Image-Reporting and Data System

1. Methods

1.1 Selection criteria

Table 2. *Selection criteria*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention or diagnostic accuracy	
Study design	Cross-sectional head-to-head (fully paired) studies, or Randomised controlled trials or Systematic reviews thereof	
Population	Biopsy naïve individuals with a PI-RADS or Likert score 3 lesion on mpMRI	> 10% of population have undergone prior biopsy and outcomes not stratified for biopsy-naïve patients. Prostate cancer patients (restricted to radical prostatectomy specimens) Not 5-point Likert scale.
Intervention	**MRI-targeted biopsy** • minimum 2-cores, • any fusion method (software registration, cognitive, in-bore) + **12-core** or < 20-core **systematic biopsy**	Single core targeted biopsy Perilesional biopsies
Comparator	≥ 20-core systematic biopsy • includes template biopsies, • transperineal or transrectal approach **+** MRI-targeted biopsy	Systematic or template biopsy < 20 cores. Systematic biopsy excludes regions sampled by targeted biopsy Biopsy approach differed from that used for the intervention
Outcome	Detection of: **ISUP grade ≥ 2 prostate cancer (primary outcome)**, or ISUP grade ≥ 3 prostate cancer, or ISUP grade 1 prostate cancer	ISUP grade ≥ 2 combined with a subgroup of ISUP grade 1 for example • Max CCL ≥5 mm for Gleason score 6 disease
Analyses	Per-patient	Per-lesion
Publication date	From 2010 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

CCL = cancer core length; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PI-RADS = Prostate Image-Reporting and Data System

1.2 Definitions and terminology

For the purposes of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Clinically significant prostate cancer refers to *ISUP grade ≥ 2 prostate cancer.*

ISUP grade ≥ 2 prostate cancer (clinically significant prostate cancer) is prostate cancer scored as Gleason Score 7(3+4) or higher on histopathological findings (Epstein 2016).

ISUP grade ≥ 3 prostate cancer is prostate cancer scored as Gleason Score 7(4+3) or higher on histopathological findings (Epstein 2016).

ISUP grade 1 prostate cancer is prostate cancer scored as Gleason Score 6(3+3) on histopathological findings (Epstein 2016).

Multi-parametric MRI (mpMRI) refers to an imaging protocol used to detect and characterise tissue abnormalities to determine the presence and severity of cancer. Prostate mpMRI acquisition includes T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging.
Systematic biopsy refers to a biopsy in which cores are taken from areas of the prostate according to a template or pattern and includes saturation biopsies.
Targeted biopsy refers to a biopsy in which cores are taken from lesions identified on MRI as suspicious of harbouring significant cancer. Cognitive, software registration or in-bore image fusion techniques are used to identify lesions for biopsy.

- Cognitive image fusion refers to the operator visually fusing MRI images and real time ultrasound pictures.
- Software registration image fusion refers to using software to fuse uploaded MRI images to real time ultrasound.
- In-bore image fusion refers to fusing prior MRI images and a real time MRI during biopsy.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website

- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and as the evidence for mpMRI-targeted biopsy continues to evolve, be based on literature published up until 2022 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

A search for systematic reviews of prostate mpMRI published from 2010 onwards in Medline, Embase and Cochrane Systematic Review databases (search strategies in Appendix A) yielded 302 records. Two relevant systematic reviews were identified:

- Haider et al (2021), a systematic review for the Cancer Care Ontario Guideline 27-2 Version 2: *Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer,* captured relevant literature published from 1st May 2013 to 1st September 2020
- Drost et al (2019) captured relevant literature published from 1st January 1990 to 31st July 2018

We assessed studies included in the Haider 2021 and Drost 2019 systematic reviews for inclusion in our systematic review, and designed searches to identify randomised controlled trials and head-to-head (paired) studies or systematic reviews thereof published from 2018 onwards. Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations), Embase and Cochrane CENTRAL databases were searched initially on 6th December 2023 combining text terms and database-specific subject headings for

prostate cancer, multiparametric MRI and biopsy, and a filter for randomised controlled trials (RCT / CCT - MEDLINE, Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 2024-07-30.). Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st November 2024. The searches were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the searches is included as Appendix A. Reference lists of recent relevant guidelines and systematic reviews were checked for potential additional articles. If no relevant studies were found, in the case an article reported near-complete data to meet criteria for inclusion we contacted authors once via email to request additional data, e.g., if PIRADS-stratified outcome data were not available for a reported biopsy-naïve subgroup.

1.5 Data extraction and analyses

Extraction of the following study characteristics was planned: Country and year of publication, study setting and period, participant eligibility and age, details of mpMRI, MRI-targeted biopsy and systematic biopsy, and relevant comparisons and outcomes reported. We planned to calculate clinically significant prostate cancer undetected, and the relative sensitivity of the different biopsy approaches and to undertake pooled analyses if there were two or more studies reporting the same outcome.

1.6 Risk of bias assessments

Independent assessments of the risk of bias by two reviewers using Cochrane Collaboration Risk of Bias-II tool (Sterne 2019) for randomised controlled trials and using a modified version of the Quality of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool (Whiting 2011) were planned.

1.7 GRADE assessment of the certainty of the evidence

GRADE assessments were planned to assess the certainty of the body of evidence for each outcome. (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence). The certainty of the body of evidence would be rated *high*, *moderate*, *low* or *very low* based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Grade Handbook 2013), Schunemann 2020a, Schunemann 2020b and Schunemann 2022. As per GRADE guidance, studies started with a high level of certainty in the evidence and were to be downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

1.8 Clinical trial registry searches

Potentially relevant ongoing and unpublished trials were identified from literature and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 29 October 2024. The clinical trial registries were searched with the search terms listed below:

Clinicaltrials.gov using the terms:

“prostate cancer” and “multiparametric MRI” and “biopsy”

“prostate cancer” and “MRI” and “biopsy”
“prostate cancer” and “magnetic resonance imaging” and “biopsy”

International Clinical Trials Registry Platform using the terms:
“prostate cancer” and “multiparametric MRI” and “biopsy”
“prostate cancer” and “MRI” and “biopsy”
“prostate cancer” and “magnetic resonance imaging” and “biopsy”

Australia and New Zealand Clinical Trial Registry using the terms:
“prostate cancer” and “magnetic resonance imaging”
“prostate cancer” and “multiparametric MRI”
“prostate cancer” and “MRI”
“prostate cancer” and “biopsy”

2. Results

2.1 Guidelines searches

One potentially relevant guideline was identified which was based on systematic reviews of the literature published up until 2022 or later. It was not considered for adoption as the systematic reviews were not accessible (Appendix B).

2.2 Literature searches

The systematic search for studies published from 2018 onwards identified 5908 unique records to November 1st, 2024 (Figure 1). Of these, 284 full text articles were retrieved for a more detailed evaluation. 36 studies published to 2020 included in the Haider 2021 and Drost 2019 systematic reviews, and one article identified in a reference list were also assessed for inclusion. We found no randomised control trials or head-to-head (paired) studies that reported detection of clinically significant prostate cancer defined as ISUP grade ≥ 2 for the population and comparisons of interest. We contacted authors of two studies reporting near-complete data for additional information. Petov 2023 provided additional data, however the study was excluded as comparator data (combined systematic and MRI-targeted biopsy) results were unable to be extracted. Novara 2023 reported data for the population and comparisons of interest, however clinically significant prostate cancer was defined as Gleason score ≥ 4+3 (ISUP grade ≥3) and/or maximum core involvement 6 mm. The authors did not respond to our request for ISUP grade ≥ 2 data, and therefore the study was excluded.
There were no studies that included Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.
The retrieved articles that were not included in this systematic review and the reasons for their exclusion are documented in Appendix C. The main reasons for exclusion were irrelevant comparator or irrelevant population.

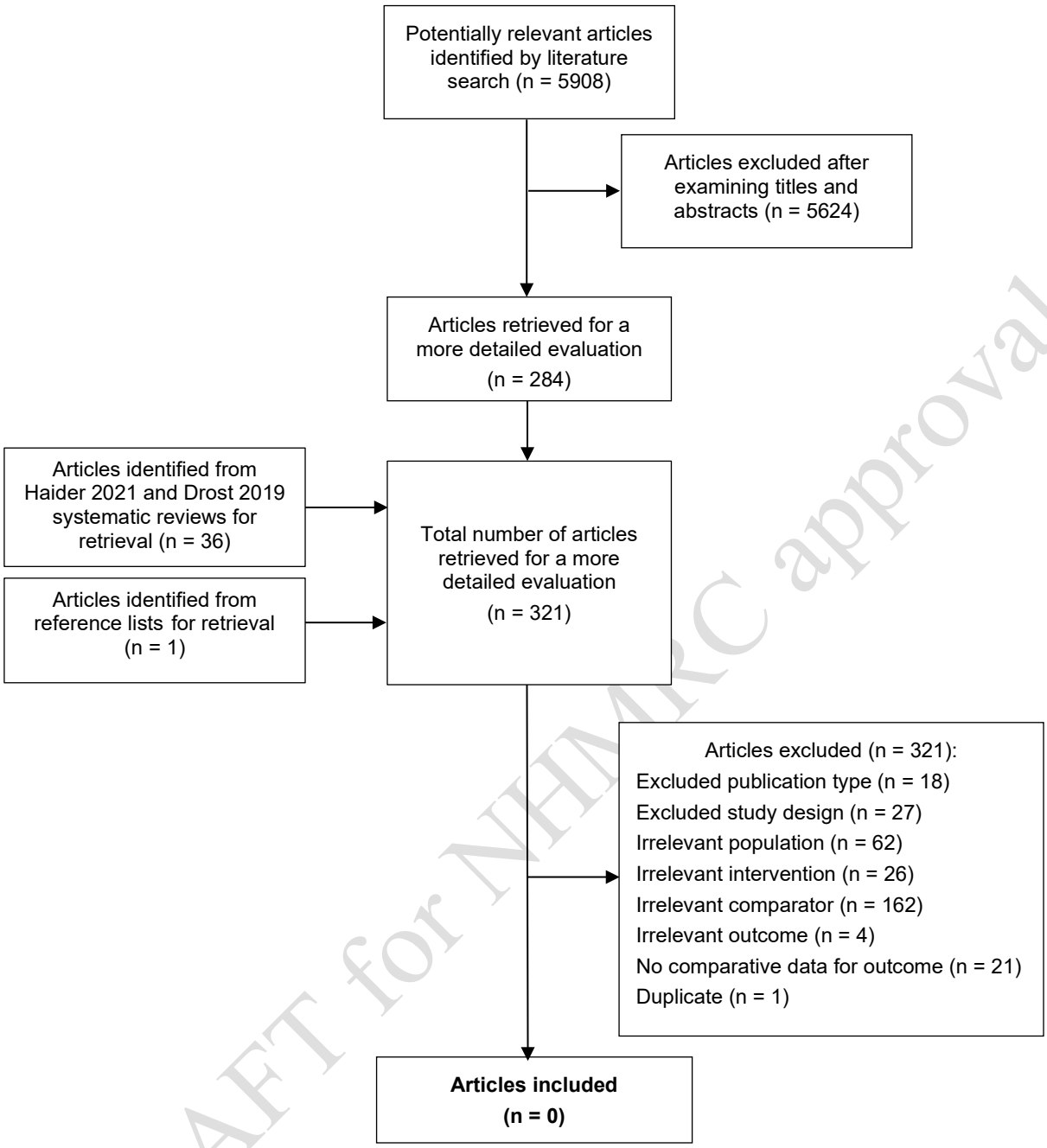

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

3. Ongoing clinical trials

One potentially relevant ongoing trial protocol was identified by searches of clinical trial registries or literature searches.

Table 3. *Summary of potentially relevant ongoing randomised controlled trial comparing biopsy protocols with lower numbers of biopsy cores which include a targeted biopsy with a systematic biopsy of ≥ 20 cores with or without MRI-targeted biopsy*

Study ID Publications	Study name, location and study design	Start date	Planned completion date	Population	Intervention	Comparator	Outcomes
NCT04685928	Extended Systematic Versus Mri-Assisted pRostate Transperineal Biopsy (SMART) trial Hong Kong RCT – 2 arms	2021 Recruiting	2025	Biopsy-naïve men aged ≥18 years with clinical suspicion of prostate cancer based on elevated PSA (4-20 ng/ml) +/- abnormal DRE	mpMRI If PIRADS score 3-5, transperineal MRI-targeted biopsy (3-4 cores) + 12-core systematic biopsy (sparing MRI targets) If PIRADS score 1-2, no biopsy	No mpMRI Transperineal 24-core systematic biopsy for all men	*Primary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection *Secondary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection of MRI-targeted biopsy only vs systematic biopsy only Clinically insignificant prostate cancer (ISUP Grade 1) detection Biopsies avoided among mpMRI negative men Maximum cancer core length Adverse events at 30 days post biopsy Health-related quality of life Cost per diagnosis of cancer

DRE = digital rectal examination; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PIRADS = Prostate Image-Reporting and Data System; RCT = randomised controlled trial

REFERENCES:

Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019 Apr 25;4(4):CD012663.

Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol. 2016 Feb;40(2):244-52.

Haider, M.A. et al. Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer: an Updated Systematic Review. Clinical Oncology. 2021 Dec; 33(12):e599 - e612.

Novara G, Zattoni F, Zecchini G, et al. Role of targeted biopsy, perilesional biopsy, and random biopsy in prostate cancer diagnosis by mpMRI/transrectal ultrasonography fusion biopsy. World J Urol. 2023;41(11):3239-3247.

Petov V, Bazarkin A, Morozov A, et al. A Prospective Comparison of Transrectal Standard, Cognitive, Transperineal Fusion, and Mapping Prostate Biopsy for Cancer Detection. J Endourol. 2023;37(8):940-947.

Schunemann H, Brozek J, Guyatt G, Oxman A, eds. Handbook for grading the quality of evidence and the strength of recommendation using the GRADE approach. Updated October 2013.

Schunemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 1. Study design, risk of bias and indirectness in rating the certainty of evidence across a body of evidence for test accuracy. J. Clin. Epidemiol. 2020a;122:129-141

Schunemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 2. Test accuracy: inconsistency, imprecision, publication bias, and other domains for rating the certainty of evidence and present it in evidence profiles and summary of findings tables. J. Clin. Epidemiol. 2020b;122:142-152.

Schunemann HJ, Neumann I, Hultcrantz M et al. 2022. GRADE guidance 35: Update on rating imprecision for assessing contextualized certainty of evidence and making decisions. J. Clin. Epidemiol. 150:225-242.

Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

Whiting PF, Rutjes AW, Westwood ME, QUADAS-2 Group, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36.

APPENDICES

A.1 Search strategies for systematic reviews published 2010 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2010 -Current"
20	(Systematic* adj3 review*).tw.
21	(meta-analys* or meta analys*).tw.
22	20 or 21
23	19 and 22
24	remove duplicates from 23

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2010 and Jan 2025, in Cochrane Reviews (Word variations have been searched)

A.2a Search strategies for primary randomised controlled trials published 2018 onwards

Databases: Medline, Embase and Cochrane Central Register of Controlled Trials databases (via Ovid platform)

#	Searches
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
21	Randomized Controlled Trial/
22	exp Randomized Controlled Trials as Topic/
23	"Randomized Controlled Trial (topic)"/
24	Controlled Clinical Trial/
25	exp Controlled Clinical Trials as Topic/
26	"Controlled Clinical Trial (topic)"/
27	Randomization/
28	Random Allocation/
29	Double-Blind Method/
30	Double Blind Procedure/
31	Double-Blind Studies/
32	Single-Blind Method/
33	Single Blind Procedure/
34	Single-Blind Studies/
35	Placebos/
36	Placebo/
37	Control Groups/
38	Control Group/
39	(random* or sham or placebo*).ti,ab,hw,kf.
40	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
41	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
42	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
43	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
44	allocated.ti,ab,hw.
45	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
46	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
47	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
48	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
49	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
50	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
51	or/20-50
52	19 and 51
53	remove duplicates from 52

A.2b Search strategies for primary studies published 2018 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	Searches
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	from 19 keep 1-6000
21	remove duplicates from 20
22	from 19 keep 6001-7458
23	remove duplicates from 22
24	21 or 23
25	remove duplicates from 24

Appendix B: Potentially relevant prostate cancer early detection and management guidelines reportedly based on systematic reviews

Developer	Publication or link	Title	Year	Reasons for not adopting
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	Systematic reviews of the evidence were not accessible.

Appendix C: Excluded Studies

Article	DOI	Reason for exclusion
Articles from primary studies search for randomised controlled trials		
Ahlberg 2019	https://dx.doi.org/10.1136/bmjopen-2018-027860	Irrelevant population
Alberts 2019	https://dx.doi.org/10.1016/j.eururo.2018.07.031	Excluded study design
Alkema 2022	https://dx.doi.org/10.1016/j.euros.2022.08.005	Excluded study design
Alterbeck 2024	https://dx.doi.org/10.1111/bju.16143	Excluded study design

Amin 2020	https://dx.doi.org/10.1111/bju.14999	Excluded study design
Arsov 2022	https://dx.doi.org/10.1002/ijc.33940	Irrelevant population
Auvinen 2024	https://dx.doi.org/10.1001/jama.2024.3841	Irrelevant population
Baccaglini 2021	https://dx.doi.org/10.1016/j.clgc.2020.06.008	Excluded study design
Bates 2023	https://doi.org/10.1016/S0302-2838(23)00144-6	Excluded publication type
Bjornebo 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.7131	Irrelevant population
Boschheidgen 2024	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Excluded study design
Bratt 2019	https://dx.doi.org/10.1016/j.eururo.2019.02.035	Irrelevant population
Bryant 2023	https://dx.doi.org/10.1111/bju.15978	Irrelevant comparator
Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Excluded study design
Checcucci 2022	https://doi.org/10.1016/S2666-1683(22)01175-2	Excluded publication type
Checcucci 2023	https://doi.org/10.21873/anticanres.16021	Excluded publication type
Checcucci 2024	https://doi.org/10.1016/S0302-2838(22)00538-3	Excluded publication type
Checcucci 2022	https://doi.org/10.1097/JU.0000000000002555.11	Excluded publication type
Chen 2018	https://dx.doi.org/10.1016/j.ajur.2017.07.001	Excluded study design
ChiCTR2000036915 2020	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000036915	Excluded publication type
Choi 2019	https://dx.doi.org/10.1016/j.clgc.2018.09.007	Excluded study design
Dadpour 2023	https://pubmed.ncbi.nlm.nih.gov/37645612/	Irrelevant population
DRKS00032422 2023	https://drks.de/search/en/trial/DRKS00032422	Excluded publication type
Eineluoto 2018	https://dx.doi.org/10.1016/j.euo.2018.02.005	Excluded study design
Eklund 2021	https://dx.doi.org/10.1056/NEJMoa2100852	Irrelevant comparator
Elwenspoek 2019	https://dx.doi.org/10.1001/jamanetworkopen.2019.8427	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Excluded study design
Ettala 2022	https://dx.doi.org/10.1136/bmjopen-2021-053118	Irrelevant intervention
Exterkate 2020	https://dx.doi.org/10.1016/j.euo.2019.06.005	Irrelevant population
Exterkate 2023	https://dx.doi.org/10.1111/bju.15876	Irrelevant population
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	Irrelevant comparator
Ghai 2024	https://dx.doi.org/10.1148/radiol.231948	Irrelevant population
Guo 2024	https://dx.doi.org/10.1186/s13244-024-01699-4	Excluded study design
Hamid 2019	https://dx.doi.org/10.1016/j.eururo.2018.08.007	Excluded study design
He 2021	https://dx.doi.org/10.1136/bmjopen-2020-041427	Excluded publication type
Hu 2020	https://dx.doi.org/10.1007/s00261-019-02370-z	Irrelevant comparator
Hugosson 2022	https://dx.doi.org/10.1056/NEJMoa2209454	Irrelevant comparator
Hugosson 2019	https://doi.org/10.1016/S1569-9056(19)31108-X	Excluded publication type
Israel 2022	https://dx.doi.org/10.1111/bju.15562	Excluded study design
ISRCTN60263108 2022	https://www.isrctn.com/ISRCTN60263108	Excluded publication type
Izadpanahi 2021	https://dx.doi.org/10.1038/s41391-021-00366-9	Irrelevant comparator
Jahnen 2024	https://doi.org/10.1016/S0302-2838(24)00876-5	Excluded publication type
Jahnen 2023	https://doi.org/10.1016/S0302-2838(23)00355-X	Excluded publication type
Jiang 2024	https://dx.doi.org/10.1016/j.euo.2023.12.002	Irrelevant comparator
Kasivisvanathan 2018	https://dx.doi.org/10.1056/NEJMoa1801993	Irrelevant comparator
Kasivisvanathan 2019	https://dx.doi.org/10.1016/j.eururo.2019.04.043	Irrelevant comparator
Kasivisvanathan 2022	https://dx.doi.org/10.1371/journal.pone.0263345	Irrelevant comparator
Kelly 2023	https://dx.doi.org/10.1016/j.euros.2023.05.002	Excluded study design

Klotz 2020	https://dx.doi.org/10.1016/j.eururo.2019.10.007	Irrelevant population
Klotz 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7589	Irrelevant comparator
Klotz 2022	https://dx.doi.org/10.1016/j.cct.2021.106618	Irrelevant intervention
Klotz 2024	https://dx.doi.org/10.1016/j.euo.2023.09.013	Irrelevant population
Kohestani 2021	https://dx.doi.org/10.1080/21681805.2021.1881612	Irrelevant population
Kruger-Stokke 2021	https://dx.doi.org/10.3389/fonc.2021.745657	Irrelevant comparator
Liu 2024	https://dx.doi.org/10.1136/bmjopen-2023-080593	Excluded study design
Luzzago 2021	https://dx.doi.org/10.1038/s41391-020-00290-4	Excluded study design
Mian 2024	https://dx.doi.org/10.1097/JU.0000000000003979	Excluded study design
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	Excluded study design
Morote 2024	https://dx.doi.org/10.3390/cancers16132306	Excluded study design
NCT03572946 2018	https://clinicaltrials.gov/study/NCT03572946	Excluded publication type
NCT04993508 2021	https://clinicaltrials.gov/study/NCT04993508	Excluded publication type
NCT04953351 2021	https://clinicaltrials.gov/study/NCT04953351	Excluded publication type
NCT06303622 2024	https://clinicaltrials.gov/study/NCT06303622	Excluded publication type
NCT03632655 2018	https://clinicaltrials.gov/study/NCT03632655	Excluded publication type
NICE 2019	https://www.ncbi.nlm.nih.gov/books/NBK576979/	Excluded study design
Nordstrom 2021	https://dx.doi.org/10.1016/S1470-2045%2821%2900348-X	Irrelevant population
Nordstrom 2024	https://dx.doi.org/10.1001/jamanetworkopen.2023.54577	Irrelevant population
Panebianco 2018	https://dx.doi.org/10.1016/j.euo.2018.03.008	Irrelevant outcome
Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Porpiglia 2023	https://dx.doi.org/10.23736/S2724-6051.22.05189-8	Irrelevant comparator
Porreca 2020	https://dx.doi.org/10.1097/MD.0000000000022059	Irrelevant population
Prince 2021	https://dx.doi.org/10.2214/AJR.20.25207	Excluded study design
Rabah 2021	https://dx.doi.org/10.15537/smj.2021.42.6.20200771	Irrelevant comparator
Rai 2021	https://dx.doi.org/10.1016/j.euo.2020.12.012	Irrelevant comparator
Rakauskas 2023	https://dx.doi.org/10.1371/journal.pone.0280262	Excluded study design
Russo 2021	https://dx.doi.org/10.1016/j.euo.2021.03.007	Irrelevant comparator
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	Irrelevant population
Schiavina 2021	https://dx.doi.org/10.1016/j.urolonc.2020.10.018	Irrelevant population
Szewczyk-Bieda 2019	https://dx.doi.org/10.1186/s13063-019-3746-0	Irrelevant comparator
Wagensveld 2021	https://doi.org/10.1016/S0302-2838(21)01279-3	Excluded publication type
Wang 2023	https://dx.doi.org/10.1007/s00345-022-04086-0	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.eururo.2018.11.040	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.euo.2019.08.007	Irrelevant population
Wei 2023	https://dx.doi.org/10.1148/radiol.221428	Irrelevant population
Woo 2019	https://dx.doi.org/10.1016/j.euo.2019.05.004	Irrelevant comparator
Yang 2024	https://dx.doi.org/10.1016/j.acra.2024.08.027	Excluded study design
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Excluded study design
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant comparator
Zhang 2022	https://dx.doi.org/10.3389/fsurg.2022.1058288	Irrelevant comparator
Zhu 2018	https://dx.doi.org/10.7150/jca.24690	Irrelevant comparator
Articles from primary studies search and citation search for head-to-head studies		
Agrotis 2023	https://dx.doi.org/10.1002/jcu.23497	Irrelevant comparator

Ahdoot 2020	https://dx.doi.org/10.1056/NEJMoa1910038	Irrelevant comparator
Ahmed 2017	https://doi.org/10.1016/S0140-6736(16)32401-1	Irrelevant intervention
Alqahtani 2021	https://dx.doi.org/10.3390/cancers14010001	Irrelevant comparator
Alqahtani 2022	https://dx.doi.org/10.3390/cancers14010001	Irrelevant comparator
An 2024	https://dx.doi.org/10.1007/s00345-024-04947-w	Irrelevant comparator
Andras 2019	https://dx.doi.org/10.11152/mu-1705	Irrelevant comparator
Araujo 2023	https://dx.doi.org/10.4081/aiua.2023.11830	Irrelevant comparator
Avolio 2023	https://dx.doi.org/10.1007/s00345-023-04480-2	Irrelevant comparator
Bangash 2021	https://dx.doi.org/10.53350/pjmhs2115102625	Irrelevant population
Barrett 2019	https://dx.doi.org/10.1016/j.crad.2019.06.004	Irrelevant comparator
Barrett 2016	https://doi.org/10.1007/s00345-015-1650-0	Irrelevant population
Barth 2021	https://dx.doi.org/10.1016/j.ejro.2021.100332	Irrelevant intervention
Bass 2018	https://dx.doi.org/10.1136/bmjopen-2018-024941	Irrelevant comparator
Bastian-Jordan 2018	https://dx.doi.org/10.1111/1754-9485.12678	Irrelevant comparator
Bhat 2020	https://dx.doi.org/10.1080/13685538.2019.1641796	Irrelevant population
Boeve 2023	https://dx.doi.org/10.1111/bju.16041	Irrelevant intervention
Bonekamp 2019	https://dx.doi.org/10.1007/s00330-018-5751-1	Irrelevant intervention
Borghesi 2021	https://dx.doi.org/10.23736/S2724-6051.20.03758-3	Irrelevant comparator
Bosaily 2020	https://dx.doi.org/10.1016/j.eururo.2020.03.002	Irrelevant intervention
Boschheidgen 2023	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Irrelevant comparator
Bourgeno 2024	https://dx.doi.org/10.1016/j.euo.2024.01.007	Irrelevant comparator
Briggs 2021	https://dx.doi.org/10.1016/j.urology.2021.04.040	Irrelevant population
BrizmohunAppayya 2018	https://dx.doi.org/10.1259/bjr.20170645	Irrelevant population
Camacho 2023	https://doi.org/10.1002/bco2.231	Irrelevant comparator
Cetin 2023	https://dx.doi.org/10.18621/eurj.1198992	Irrelevant population
Chaloupka 2023	https://dx.doi.org/10.1111/bju.16248	Irrelevant comparator
Chandra Engel 2024	https://doi.org/10.1016/j.euo.2024.10.002	Irrelevant comparator
Chau 2018	https://dx.doi.org/10.1016/j.ijso.2018.01.002	Irrelevant population
Chau 2024	https://dx.doi.org/10.1007/s11845-024-03637-1	Irrelevant comparator
Checcucci 2020	https://dx.doi.org/10.23736/S0393-2249.20.03958-2	Irrelevant comparator
Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Irrelevant comparator
Cheng 2021	https://dx.doi.org/10.3389/fonc.2021.643051	Irrelevant comparator
Cheng 2022	https://dx.doi.org/10.1080/08941939.2020.1825884	Irrelevant comparator
Choomark 2023	https://dx.doi.org/10.33192/smj.v75i11.265361	Irrelevant comparator
Connor 2020	https://dx.doi.org/10.1097/JU.0000000000001184	Irrelevant comparator
D'Agostino 2019	https://dx.doi.org/10.4081/aiua.2019.2.87	Irrelevant comparator
D'Agostino 2020	https://dx.doi.org/10.4081/aiua.2019.4.211	Irrelevant comparator
Dahl 2022	https://dx.doi.org/10.1016/j.urolonc.2022.07.011	Irrelevant population
Dahl 2024	https://dx.doi.org/10.1016/j.urolonc.2023.11.004	Irrelevant population
Del Monte 2018	https://dx.doi.org/10.1007/s11547-017-0825-8	Irrelevant comparator
Dell'Oglio 2020	https://dx.doi.org/10.1016/j.euo.2019.03.002	Irrelevant comparator
Demirtas 2019	https://dx.doi.org/10.7759/cureus.6160	Irrelevant comparator
Deniffel 2022	https://dx.doi.org/10.1007/s00330-022-08822-3	Irrelevant population
Dhir 2023	https://dx.doi.org/10.1016/j.urology.2023.04.017	Irrelevant comparator

Diez 2024	https://doi.org/10.1007/s00345-024-05233-5	No comparative data for outcome
Donato 2020	https://dx.doi.org/10.1007/s00345-019-02774-y	Irrelevant comparator
Dragoescu 2023	https://dx.doi.org/10.3390/diagnostics13081373	Irrelevant comparator
Droghetti 2023	https://dx.doi.org/10.1007/s00345-022-04229-3	Irrelevant comparator
Eldred-Evans 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7456	Irrelevant comparator
Elfatairy 2019	https://dx.doi.org/10.1148/rycan.2019190016	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.2967/jnumed.121.263448	Excluded study design
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Irrelevant intervention
Emmett 2023	https://dx.doi.org/10.2967/jnumed.123.266164	Irrelevant intervention
Falagario 2021	https://dx.doi.org/10.1111/iju.14385	Irrelevant comparator
Fleville 2024	https://dx.doi.org/10.1097/JU.0000000000004226	Irrelevant comparator
Freifeld 2019	https://dx.doi.org/10.1016/j.urolonc.2018.10.009	Irrelevant comparator
Fulco 2021	https://dx.doi.org/10.3390/cancers13194833	Irrelevant comparator
Furrer 2022	https://dx.doi.org/10.1111/ans.17713	Irrelevant comparator
Gavin 2020	https://dx.doi.org/10.1016/j.euros.2020.07.001	Irrelevant population
Gayet 2020	https://dx.doi.org/10.1155/2020/4626781	Irrelevant comparator
Gomez-Gomez 2021	https://dx.doi.org/10.3390/diagnostics11081335	Irrelevant comparator
Gorin 2020	https://dx.doi.org/10.1007/s00345-019-02992-4	Irrelevant comparator
Gortz 2022	https://dx.doi.org/10.3390/cancers14040886	Irrelevant population
Grey 2022	https://dx.doi.org/10.1016/S1470-2045(22)00016-X	Irrelevant comparator
Gross 2020	https://dx.doi.org/10.1097/JU.0000000000000534	Irrelevant comparator
Gunzel 2022	https://dx.doi.org/10.1007/s11255-022-03309-y	Irrelevant comparator
Hagens 2022	https://dx.doi.org/10.1016/j.euros.2022.07.006	Irrelevant comparator
Hagens 2022	https://dx.doi.org/10.1016/j.euros.2022.04.001	Irrelevant population
Hansen 2020	https://dx.doi.org/10.1111/bju.14865	Irrelevant population
Hansen 2018	https://dx.doi.org/10.1111/bju.14049	Irrelevant intervention
Henning 2021	https://dx.doi.org/10.1016/j.urolonc.2020.11.018	Irrelevant comparator
Hepp 2022	https://dx.doi.org/10.1007/s00345-022-03991-8	Irrelevant population
Ho 2023	https://dx.doi.org/10.1016/j.urolonc.2023.11.005	Irrelevant population
Hofbauer 2022	https://dx.doi.org/10.1111/bju.15635	Irrelevant population
Hogan 2022	https://dx.doi.org/10.1177/20514158221084820	No comparative data for outcome
Hogan 2024	https://dx.doi.org/10.1177/20514158221084820	Duplicate
Hou 2022	https://dx.doi.org/10.1038/s41391-021-00489-z	Irrelevant comparator
Hsi 2023	https://dx.doi.org/10.1002/bco2.184	No comparative data for outcome
Hsieh 2022	https://dx.doi.org/10.31083/j.jomh1806127	Irrelevant population
Huang 2022	https://dx.doi.org/10.2147/CMAR.S350701	Irrelevant comparator
Hubbard 2021	https://pubmed.ncbi.nlm.nih.gov/34786148/	Irrelevant population
Hung 2024	https://dx.doi.org/10.1016/j.urology.2023.11.039	Irrelevant comparator
Jahnen 2023	https://dx.doi.org/10.1007/s00345-023-04564-z	Irrelevant comparator
Kachanov 2022	https://dx.doi.org/10.1097/JU.0000000000002248	Irrelevant comparator
Kalapara 2022	https://dx.doi.org/10.1016/j.euo.2021.02.006	No comparative data for outcome
Kam 2018	https://dx.doi.org/10.1016/j.prnil.2017.10.003	Irrelevant population

Kasivisvanathan 2024	https://doi.org/10.1016/j.eururo.2024.08.022	Irrelevant comparator
Kato 2021	https://dx.doi.org/10.3390/curroncol28020123	Irrelevant comparator
Kaufmann 2022	https://dx.doi.org/10.1002/pros.24286	Irrelevant population
Khoo 2021	https://dx.doi.org/10.1097/JU.0000000000001476	Irrelevant population
Kim 2021	https://dx.doi.org/10.1007/s00330-020-07167-z	Irrelevant comparator
Kim 2022	https://dx.doi.org/10.1097/JU.0000000000002168	Irrelevant intervention
Kong 2023	https://dx.doi.org/10.1177/20514158211065946	No comparative data for outcome
Kortenbach 2021	https://dx.doi.org/10.1016/j.heliyon.2021.e08325	No comparative data for outcome
Krausewitz 2023	https://dx.doi.org/10.1007/s00345-022-04230-w	Irrelevant comparator
Kuhlmann 2022	https://dx.doi.org/10.1016/j.urolonc.2021.12.016	Irrelevant comparator
Kurokawa 2024	https://dx.doi.org/10.21873/anticanres.16858	Irrelevant comparator
Kwon 2023	https://dx.doi.org/10.1007/s11255-023-03674-2	No comparative data for outcome
Labra 2020	https://dx.doi.org/10.1007/s00261-020-02481-y	Irrelevant comparator
Lahoud 2021	https://dx.doi.org/10.1111/ans.16524	Irrelevant intervention
Lee 2020	https://dx.doi.org/10.1111/bju.15118	Irrelevant intervention
Lee 2021	https://dx.doi.org/10.1016/j.urolonc.2021.02.027	Irrelevant intervention
Lee 2022	https://dx.doi.org/10.1016/j.prnil.2021.08.003	Irrelevant population
Lee 2022	https://dx.doi.org/10.1038/s41391-021-00485-3	Irrelevant comparator
Leow 2023	https://dx.doi.org/10.4103/aja2021128	Irrelevant comparator
Liu 2020	https://dx.doi.org/10.1038/s41391-020-0260-0	Irrelevant comparator
Liu 2021	https://dx.doi.org/10.1259/bjr.20210312	Irrelevant comparator
Liu 2023	https://dx.doi.org/10.1002/jmri.28614	Irrelevant comparator
Lockhart 2022	https://dx.doi.org/10.1177/20514158221085081	No comparative data for outcome
Lombardo 2023	https://dx.doi.org/10.3390/life13081719	Irrelevant comparator
Lopez 2021	https://dx.doi.org/10.1111/bju.15337	No comparative data for outcome
Lovegrove 2020	https://dx.doi.org/10.1097/JU.0000000000000455	Irrelevant intervention
Lughezzani 2019	https://dx.doi.org/10.1016/j.euo.2018.10.001	Irrelevant comparator
Malewski 2023	https://dx.doi.org/10.3390/jcm12175612	Irrelevant comparator
Martin 2023	https://dx.doi.org/10.1007/s00345-023-04386-z	Irrelevant comparator
Mesko 2018	https://dx.doi.org/10.1097/COC.0000000000000308	Irrelevant comparator
Miah 2020	https://dx.doi.org/10.1007/s11701-019-00929-y	Irrelevant population
Mischinger 2018	https://dx.doi.org/10.1111/bju.14089	Irrelevant comparator
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	No comparative data for outcome
Morote 2023	https://dx.doi.org/10.3390/cancers15184543	Irrelevant comparator
Mortezavi 2018	https://dx.doi.org/10.1016/j.juro.2018.02.067	Irrelevant intervention
Neale 2020	https://dx.doi.org/10.1111/bju.15092	Irrelevant population
Noujeim 2023	https://dx.doi.org/10.1038/s41391-022-00620-8	Irrelevant comparator
Novara 2023	https://dx.doi.org/10.1007/s00345-023-04382-3	Irrelevant outcome
Oderda 2024	https://dx.doi.org/10.3390/curroncol31070308	Irrelevant comparator
Oh 2020	https://dx.doi.org/10.4111/icu.2020.61.1.28	Irrelevant intervention
Olivetta 2024	https://dx.doi.org/10.3390/diagnostics14151643	Irrelevant comparator

Osses 2018	https://dx.doi.org/10.1159/000447216	Irrelevant comparator
Pang 2021	https://dx.doi.org/10.12998/wjcc.v9.i36.11183	Irrelevant comparator
Park 2020	https://dx.doi.org/10.3390/jcm9020530	Irrelevant comparator
Patel 2018	https://dx.doi.org/10.1016/j.euo.2018.03.009	Irrelevant comparator
Patel 2022	https://dx.doi.org/10.1097/JU.0000000000002120	Irrelevant comparator
Pepe 2022	https://dx.doi.org/10.21873/anticanres.15785	Irrelevant comparator
Petov 2023	https://dx.doi.org/10.1089/end.2022.0780	Irrelevant comparator
Phelps 2023	https://dx.doi.org/10.1007/s00261-022-03775-z	Irrelevant comparator
Ploussard 2019	https://dx.doi.org/10.1007/s00345-018-2399-z	Excluded study design
Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Pratihar 2023	https://dx.doi.org/10.4103/iju.iju_147_23	Irrelevant comparator
Rachubinski 2022	https://dx.doi.org/10.1097/JU.0000000000002921	Irrelevant population
Radtke 2019	https://dx.doi.org/10.1371/journal.pone.0221350	No comparative data for outcome
Rajendran 2024	https://dx.doi.org/10.1093/bjr/tqad027	No comparative data for outcome
Ruan 2023	https://dx.doi.org/10.1007/s00261-023-03894-1	Irrelevant comparator
Saba 2020	https://dx.doi.org/10.1097/JU.0000000000000622	No comparative data for outcome
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	No comparative data for outcome
Sanguedolce 2024	https://doi.org/10.1016/j.euo.2024.10.006	Irrelevant population
Sathianathen 2018	https://dx.doi.org/10.1038/s41391-018-0065-6	Irrelevant comparator
Sathianathen 2019	https://dx.doi.org/10.1111/bju.14617	Irrelevant comparator
Schelb 2019	https://dx.doi.org/10.1148/radiol.2019190938	Irrelevant outcome
Schmid 2023	https://dx.doi.org/10.1002/pros.24435	No comparative data for outcome
Senoglu 2022	https://dx.doi.org/10.4274/uob.galenos.2021.2021.4.1	Irrelevant comparator
Seref 2022	https://dx.doi.org/10.1002/pros.24255	Irrelevant population
Shefler 2024	https://dx.doi.org/10.1016/j.urolonc.2024.01.026	Irrelevant comparator
Siddiqui 2023	https://dx.doi.org/10.1038/s41391-023-00660-8	Irrelevant outcome
Sigle 2021	https://dx.doi.org/10.3390/cancers13102502	Irrelevant population
Sigle 2022	https://dx.doi.org/10.3390/cancers14215230	Irrelevant population
Sigle 2023	https://dx.doi.org/10.1016/j.euf.2023.01.020	Irrelevant population
Sivaraman 2022	https://dx.doi.org/10.4103/iju.iju_222_21	No comparative data for outcome
Song 2020	https://dx.doi.org/10.1097/JU.0000000000001302	Irrelevant comparator
Stabile 2021	https://dx.doi.org/10.1038/s41391-021-00371-y	Irrelevant comparator
Stavrinides 2023	https://dx.doi.org/10.1148/radiol.220762	Irrelevant population
Stevens 2023	https://dx.doi.org/10.1177/02841851231187135	Irrelevant intervention
Stone 2021	https://dx.doi.org/10.1002/bco2.111	Irrelevant intervention
Sugano 2020	https://dx.doi.org/10.1007/s11255-019-02354-4	Irrelevant comparator
Tae 2018	https://dx.doi.org/10.4111/icu.2018.59.6.363	Irrelevant comparator
Tay 2021	https://dx.doi.org/10.1002/bco2.99	Irrelevant intervention
Thangarasu 2021	https://dx.doi.org/10.2147/RRU.S300868	Irrelevant comparator
Thompson 2023	https://dx.doi.org/10.5152/tud.2023.22221	Irrelevant population
Tomioka 2023	https://dx.doi.org/10.3390/diagnostics13152608	Irrelevant comparator

Tschirdewahn 2021	https://dx.doi.org/10.1016/j.euf.2020.06.020	Irrelevant intervention
Tunc 2023	https://dx.doi.org/10.22037/uj.v20i.7610	Irrelevant comparator
Turkay 2020	https://dx.doi.org/10.1097/RUQ.0000000000000505	Irrelevant comparator
Velarde 2022	https://dx.doi.org/10.1007/s00261-021-03389-x	Irrelevant comparator
Wagaskar 2022	https://dx.doi.org/10.22037/uj.v18i.6852	No comparative data for outcome
Wang 2020	https://dx.doi.org/10.4103/aja.aja_83_19	Irrelevant comparator
Wang 2021	https://dx.doi.org/10.1186/s12894-021-00949-7	Irrelevant comparator
Washino 2018	https://dx.doi.org/10.1186/s12894-018-0361-4	Irrelevant comparator
Wei 2022	https://dx.doi.org/10.1007/s00261-022-03592-4	Irrelevant comparator
Weiser 2023	https://dx.doi.org/10.1002/jmri.28891	No comparative data for outcome
Wenzel 2021	https://dx.doi.org/10.3389/fsurg.2021.633196	Irrelevant intervention
Wong 2024	https://dx.doi.org/10.1016/j.euo.2024.01.002	No comparative data for outcome
Woo 2023	https://dx.doi.org/10.1016/j.euros.2022.11.012	Irrelevant comparator
Wu 2024	https://dx.doi.org/10.1038/s41391-023-00729-4	Irrelevant intervention
Yilmaz 2023	https://dx.doi.org/10.1148/radiol.221309	Irrelevant comparator
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Irrelevant population
Zambon 2024	https://dx.doi.org/10.1038/s41391-023-00770-3	Irrelevant comparator
Zattoni 2023	https://dx.doi.org/10.1007/s00345-023-04578-7	Irrelevant population
Zawaideh 2020	https://dx.doi.org/10.1259/bjr.20200298	Irrelevant comparator
Zhang 2018	https://dx.doi.org/10.1186/s12957-018-1367-9	Irrelevant intervention
Zhang 2019	https://dx.doi.org/10.1016/j.prnil.2018.10.001	Irrelevant comparator
Zhang 2020	https://dx.doi.org/10.1007/s10147-019-01524-9	Irrelevant population
Zhang 2020	https://dx.doi.org/10.21037/tau.2020.02.20	Irrelevant comparator
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant comparator
Zhang 2022	https://dx.doi.org/10.1186/s40644-022-00498-8	Irrelevant comparator
Zhu 2018	https://dx.doi.org/10.1097/MD.0000000000011962	Irrelevant comparator
Articles from Haider 2021 and Drost 2019 systematic reviews		
Alberts 2017	https://doi.org/10.1016/j.eururo.2017.06.019	Irrelevant comparator
Baco 2016	https://doi.org/10.1016/j.eururo.2015.03.041	Irrelevant comparator
Boesen 2018	https://doi.org/10.1001/jamanetworkopen.2018.0219	Irrelevant comparator
Borkowetz 2017	https://doi.org/10.1159/000477263	Irrelevant comparator
Borkowetz 2018	https://doi.org/10.1111/bju.14017	Irrelevant comparator
Castellucci 2017	https://doi.org/10.23736/s0393-2249.17.02845-4	Irrelevant comparator
Chen 2015	https://doi.org/10.3892%2Fetm.2014.2061	Irrelevant comparator
Cool 2016	https://doi.org/10.5489%2Fcuaj.3831	Irrelevant comparator
Delongchamps 2013	https://doi.org/10.1016/j.juro.2012.08.195	Irrelevant comparator
Distler 2017	https://doi.org/10.1016/j.juro.2017.03.130	Irrelevant population
Filson 2016	https://doi.org/10.1002/cncr.29874	Irrelevant comparator
Garcia Bennett 2017	https://doi.org/10.1016/j.diii.2017.06.010	Irrelevant comparator
Grey 2015	https://doi.org/10.1111/bju.12862	Irrelevant population
Gronberg 2018	https://doi.org/10.1016/j.eururo.2018.06.022	Irrelevant comparator
Jambor 2015	https://doi.org/10.1002/jmri.24682	Irrelevant comparator
Jambor 2017	https://doi.org/10.1002/jmri.25641	Irrelevant comparator

Kesch 2017	https://doi.org/10.1159/000458764	No comparative data for outcome
Kim 2017	https://doi.org/10.1016/j.urology.2016.08.074	Irrelevant comparator
Lee 2016	https://doi.org/10.3349/ymj.2016.57.3.565	Irrelevant comparator
Lee 2017	https://doi.org/10.3349%2Fymj.2017.58.5.994	Irrelevant comparator
Muthuveloe 2016	https://doi.org/10.5173/ceju.2016.675	Irrelevant population
Nafie 2014	https://pubmed.ncbi.nlm.nih.gov/28299763/	Irrelevant population
Okcelik 2016	https://doi.org/10.1590/s1677-5538.ibju.2015.0155	Irrelevant comparator
Panebianco 2015	https://doi.org/10.1016/j.urolonc.2014.09.013	Irrelevant comparator
Peltier 2015	https://doi.org/10.1155/2015/571708	Irrelevant comparator
Ploussard 2014	https://doi.org/10.1016/j.eururo.2012.05.049	Irrelevant population
Pokorny 2014	https://doi.org/10.1016/j.eururo.2014.03.002	Irrelevant comparator
Pressier 2019	https://doi.org/10.1016/j.euf.2019.06.015	Irrelevant comparator
Rouvière 2019	https://doi.org/10.1016/s1470-2045(18)30569-2	Irrelevant comparator
Sakar 2019	https://doi.org/10.1177/2051415819889552	Irrelevant comparator
Thompson 2016	https://doi.org/10.1016/j.juro.2015.10.140	No comparative data for outcome
Tonttilla 2016	https://doi.org/10.1016/j.eururo.2015.05.024	Irrelevant comparator
Van der Leest 2019	https://doi.org/10.1016/j.eururo.2018.11.023	Irrelevant comparator
Westoff 2019	https://doi.org/10.1016/j.urolonc.2019.07.004	Irrelevant comparator
Zalesky 2019	https://doi.org/10.5507/bp.2019.050	Irrelevant comparator
Zhang 2017	https://doi.org/10.1007/s11255-016-1484-8	Irrelevant comparator

3.15 Clinical question 9 – Prostate biopsy PICO 9C

Clinical questions:

8. *For biopsy naïve men with a PI-RADS 4-5 lesion on multiparametric MRI (mpMRI), are targeted biopsies alone acceptable/ reasonable/ adequate? (is a systematic biopsy necessary?)*
9. *For biopsy naïve men with a PI-RADS 3 lesion on mpMRI, are targeted biopsies alone acceptable/ reasonable/ adequate? (is a systematic biopsy necessary?)*

Introduction

Clinical questions 8 and 9 are each addressed by 3 systematic reviews. This is the third systematic review which addresses both clinical questions.

Systematic review report for PICO 9C: Randomised controlled trials comparing complications following a targeted biopsy with those following a systematic and targeted biopsy

Authors

Chelsea Carle, Susan Yuill, Suzanne Hughes

PICO 9C

This systematic review addresses the following PICOs which are summarised in detail in Tables 1a and 1b.

PICO 9Ca. *For men undergoing a MRI targeted biopsy, does eliminating a systematic biopsy reduce biopsy complications?*

PICO 9Cb. *For men undergoing a MRI targeted biopsy, does reducing the number of systematic biopsy cores reduce biopsy complications?*

Table 1a. *PICO 9Ca components*

Population	*Intervention*	*Comparator*	*Outcomes*	*Study design*
Individuals undergoing biopsy	MRI-targeted biopsy only	MRI-targeted biopsy + ≥ 12 core systematic biopsy OR ≥ 20 core systematic biopsy only	Hospital readmission within 30 days of biopsy Erectile dysfunction at ≥1 year	Randomised controlled trials

Table 1b. *PICO 9Cb components*

Population	*Intervention*	*Comparator*	*Outcomes*	*Study design*
Individuals undergoing biopsy	MRI-targeted biopsy + 12-core systematic biopsy	MRI-targeted biopsy + ≥ 20 core systematic biopsy OR ≥ 20 core systematic biopsy only	Hospital readmission within 30 days of biopsy Erectile dysfunction at ≥1 year	Randomised controlled trials

1. Methods

1.1 Selection criteria

Table 2. *Selection criteria*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	
Study design	RCTs or systematic reviews thereof	
Population	Individuals undergoing prostate biopsy - transperineal or transrectal approach Include men with prior negative biopsy or on active surveillance	
Intervention *PICO 9Ca*	**MRI-targeted biopsy only** • minimum 2-cores, • any fusion method (software registration, cognitive, in-bore)	Single core targeted biopsy Perilesional biopsies
Intervention *PICO 9Cb*	**MRI-targeted biopsy** • minimum 2-cores, • any fusion method (software registration, cognitive, in-bore) + **12-core (include < 20 core) systematic biopsy**	Single core targeted biopsy Perilesional biopsies
Comparator *PICO 9Ca*	**MRI-targeted biopsy** + **≥ 12 core systematic biopsy** OR **≥ 20 core systematic biopsy** alone	Perilesional biopsies The biopsy approach (transrectal or transperineal) used was different from that used for the intervention
Comparator *PICO 9Cb*	**MRI-targeted biopsy** + **≥ 20 core systematic biopsy** OR **≥ 20 core systematic biopsy** alone	Perilesional biopsies The biopsy approach (transrectal or transperineal) used was different from that used for the intervention
Outcome	**Hospital admission within 30 days** of biopsy (primary outcome) Urinary retention within 30 days of biopsy Infection requiring hospital admission within 30 days of biopsy Sepsis *For men who do not undergo definitive treatment* Erectile dysfunction at 1 year or longer	
Analyses	Per-patient	Per-lesion
Publication date	From 2010 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

MRI = magnetic resonance imaging; RCTs = randomised controlled trials

1.2 Definitions and terminology

For the purposes of this review:

Biopsy naïve refers to individuals who have not previously undergone a prostate biopsy.

Systematic biopsy refers to a biopsy in which cores are taken from all areas of the prostate according to a template or pattern and includes saturation biopsies.

Targeted biopsy refers to a biopsy in which cores are taken from lesions identified on MRI as suspicious of harbouring significant cancer. Cognitive, software registration or in-bore image fusion techniques are used to identify lesions for biopsy.

- Cognitive image fusion refers to the operator visually fusing MRI images and real time ultrasound pictures.
- Software registration image fusion refers to using software to fuse uploaded MRI images to real time ultrasound.
- In-bore image fusion refers to fusing prior MRI images and a real time MRI during biopsy.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website

- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e. be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and as the evidence for mpMRI-targeted biopsy continues to evolve, be based on literature published up until 2022 or later. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

A search for systematic reviews of prostate mpMRI and prostate biopsies published from 2010 onwards in Medline, Embase and Cochrane Systematic Review databases (search strategies in Appendix A) yielded 302 records. Two relevant systematic reviews were identified:

- Haider et al (2021), a systematic review for the Cancer Care Ontario Guideline 27-2 Version 2: *Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer,* captured relevant literature published from 1st May 2013 to 1st September 2020;
- Drost et al (2019) captured relevant literature published from 1st January 1990 to 31st July 2018.

We assessed randomised studies included in the Haider 2021 and Drost 2019 systematic reviews for inclusion in our systematic review, and designed searches to identify randomised controlled trials or systematic reviews thereof published from 2018 onwards. Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations), Embase and Cochrane CENTRAL databases were searched on 30th July 2024 combining text words and database-specific subject headings for prostate cancer, multiparametric MRI and biopsy, and a filter for randomised controlled trials (RCT / CCT - MEDLINE, Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/122. Accessed 2024-07-30.) Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st November 2024. The searches were designed to identify potentially relevant trials in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the search is included as Appendix A. Reference lists of recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

The following study characteristics were extracted: Country and year of publication, participant eligibility and age, components of intervention arm, components of comparator arm, and relevant outcomes reported. Effect estimates and 95% confidence intervals were extracted or calculated using relevant reported data. Pooled analyses were planned where there were two or more studies reporting the same outcome.

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias of critical outcomes in each included study (with independent third-reviewer adjudication as needed) using the Cochrane Collaboration Risk of Bias-II tool (Sterne 2019). The overall risk of bias for each outcome was rated low, some concerns or high for the following sources of bias; the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for each outcome determined to be critical by the Biopsy Working Group (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Schunemann 2013) and Schunemann et al 2022, and on guidance for assessing narrative syntheses provided by Murad 2017. Imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. These thresholds were determined by the Biopsy Working Group, and following GRADE guidance provided by Schunemann 2022.

Potential publication bias (or small study effects) was assessed using a Funnel Plot if 10 or more studies. Where there were less than 10 studies, clinical trial registries were searched for potentially relevant trials (see section 1.8 below for search details) commencing between 2015 and 2019 inclusive, that had not been terminated and for which results had not been published suggesting publication bias assuming studies reporting the effects of different biopsy protocols would have published results re biopsy complications and/or cancer detection rates within 5 years of the trial starting and randomised controlled trials comparing MRI targeted biopsies with systematic biopsies would be unlikely prior to 2015.

As per GRADE guidance, randomised controlled trials started with a high level of certainty in the evidence and were to be downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

Definitions of the GRADE ratings of certainty of the overall body of evidence are presented in Appendix B.

1.8 Clinical trial registry searches

Potentially relevant ongoing and unpublished trials were identified from literature searches, recent guidelines and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 29 October 2024. The clinical trial registries were searched with the search terms listed below:

Clinicaltrials.gov using the terms:
“prostate cancer” and “multiparametric MRI” and “biopsy”
“prostate cancer” and “MRI” and “biopsy”
“prostate cancer” and “magnetic resonance imaging” and “biopsy”

International Clinical Trials Registry Platform using the terms:
“prostate cancer” and “multiparametric MRI” and “biopsy”
“prostate cancer” and “MRI” and “biopsy”
“prostate cancer” and “magnetic resonance imaging” and “biopsy”

Australia and New Zealand Clinical Trial Registry using the terms:
“prostate cancer” and “magnetic resonance imaging”
“prostate cancer” and “multiparametric MRI”
“prostate cancer” and “MRI”
“prostate cancer” and “biopsy”

2. Results

2.1 Guidelines searches

One potentially relevant guideline was identified which was based on systematic reviews of the literature published up until 2022 or later. It was not considered for adoption as the systematic reviews were not accessible (Appendix C).

2.2 Literature searches

The systematic search for studies published from 2018 onwards identified 928 unique records to November 1st, 2024 (Figure 1). Of these, 90 full text articles were retrieved for a more detailed evaluation. Three studies published to 2020 included in the Haider 2021 and Drost 2019 systematic reviews were also assessed for inclusion. Two randomised controlled trials reported in two articles met criteria for inclusion in our systematic review: Hugosson 2022 (Goteborg-2 trial), and Dadpour 2023. There were no studies that reported including Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.
The retrieved articles that were not included in this systematic review and the reasons for their exclusion are documented in Appendix D. The main reasons for exclusion were excluded study design or publication type, or irrelevant comparator.

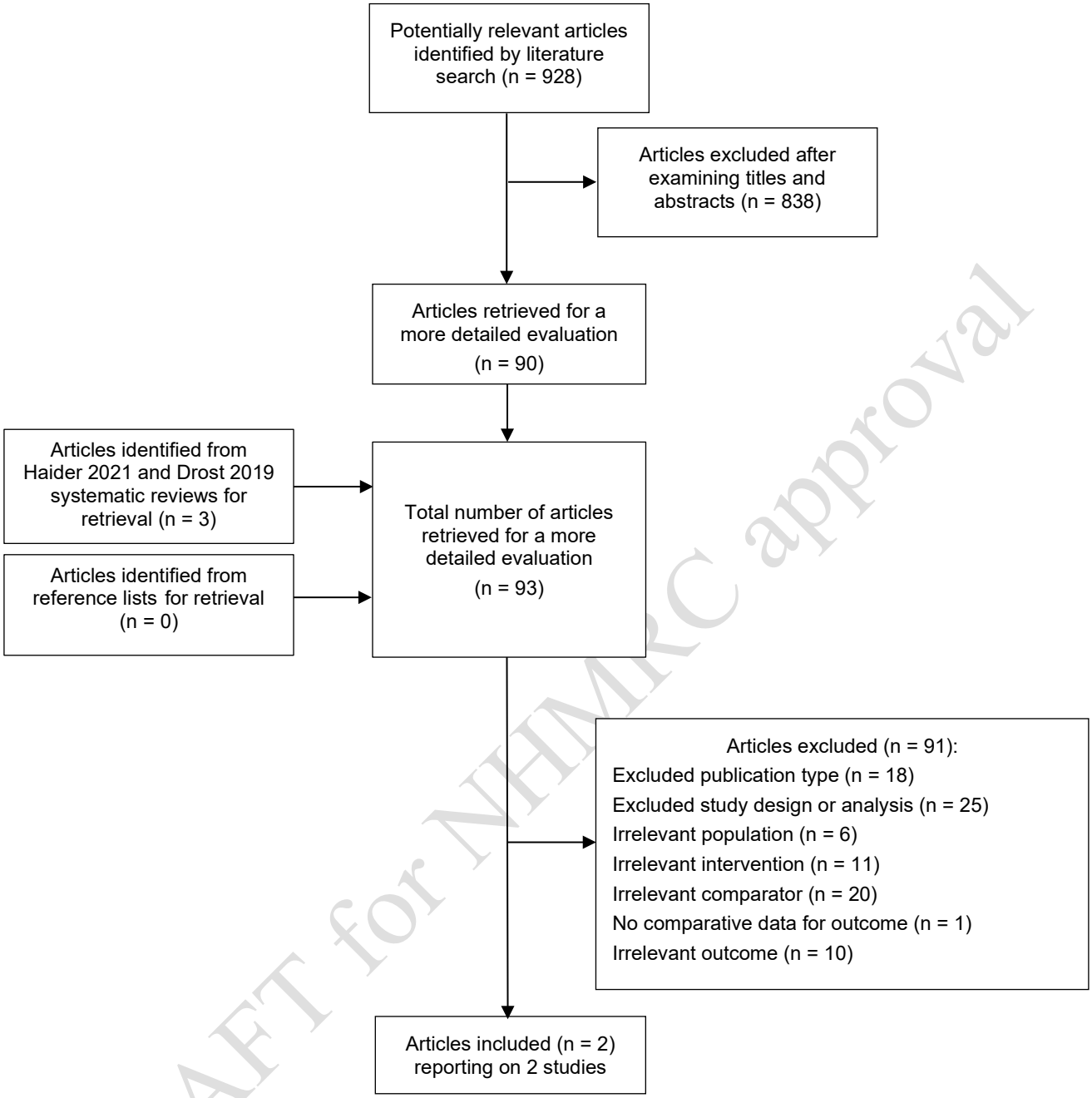

Figure 1. *Process of inclusion and exclusion of articles for the systematic review*

2.3 Characteristics of included studies

Table 3. *Study characteristics of included randomised controlled trials of individuals undergoing multiparametric MRI targeted biopsy alone or combined with systematic biopsy to determine the effect of reducing or eliminating systematic biopsy cores on post-biopsy complications*

Study	*Setting and enrolment period*	*Population*	*Intervention arm MRI-TB +/- SB*			*Control arm SB +/- MRI-TB*			*Outcomes of interest*
			N	*MRI-TB*	*SB*	*N*	*MRI-TB*	*SB*	
Hugosson 2022 Sweden *Goteborg-2 trial*	Population-based 2015-2020	Men aged 50-60 years undergoing PSA screening with PSA ≥ 3 ng/mL undergoing mpMRI and prostate biopsy N = 649 % biopsy naïve: NR Age mean: NR PSA ≥ 10 ng/mL: NR	301 (ITT) PI-RADS 3-5: 86.7% 274 (PP)	Transrectal cognitive TRUS fusion MRI-TB **if PIRADS 3-5** 4 cores per lesion N: NR	No transrectal SB unless **PSA ≥ 10 ng/mL Or PIRADS = 5** 10-12 cores N: NR	348 (ITT) PI-RADS 3-5: 39.0% 336 (PP)	Transrectal cognitive TRUS fusion MRI-TB **if PIRADS 3-5** 4 cores per lesion N: NR	Transrectal SB regardless of MRI result 10-12 cores N = 348	Hospitalisation rate at 30 days post-biopsy
Dadpour 2023 Iran	Single centre 2018-2020	Patients aged 40 to 75 years with ≥ 1 PNB (12-core TRUS SB) and PSA > 4 ng/mL undergoing second biopsy N = 105 % biopsy naïve: 0 Age mean: 62.2 years PSA level mean: 11.8 ng/mL	53	Transrectal software registration image TRUS fusion MRI-TB of PIRADS 2-5 lesions Cores per lesion NR Mean 4.6 cores per patient N = 53	Transrectal SB 12 cores N = 53	52	None No MRI or TB N = 0	Transrectal TRUS SB 20 cores N = 52	Hospitalisation for biopsy complications

ITT = intention to treat; MRI-TB = multiparametric MRI targeted biopsy; NR = not reported; PIRADS = Prostate imaging reporting and data system; PNB = prior negative biopsy; PSA = prostate specific antigen; PP = per protocol; RCT = randomised controlled trial; SB = systematic biopsy; TRUS = transrectal ultrasound-guided.

2.4 Results by outcome of interest

Results related to the detection of

Hospital admission within 30 days of biopsy (primary outcome) – Table 4

Erectile dysfunction at 1 year or longer – no results

Results for hospital admission within 30 days of biopsy

Table 4: *Hospitalisation rate within 30 days of biopsy*

Study	***Population***	***Outcome***	***Intervention arm TB +/- SB***		***Control arm SB +/- TB***		***Risk ratio* (95% CI)***
			Biopsy protocol	***Hospitalisation rate*** *Per 100 (n/N)*	***Biopsy protocol***	***Hospitalisation rate*** *Per 100 (n/N)*	
Hugosson 2022 (GOTEBORG-2) Sweden	PSA ≥ 3 ng/ml	Hospitalisations within 30 days of biopsy	TR TB (all) +/- 10-12-core SB (< 50%)	0.33 (1/301) (Hospitalisation for urosepsis)	TR 10-12-core SB (all) +/-TB (< 50%?)	1.15 (4/348) (Hospitalisations for urosepsis (2), pneumonia and acute hypertension)	0.29 (0.03, 2.57)
Dadpour 2023 Iran	≥ 1 PNB PIRADS 2-5	Biopsy complications requiring hospitalisation	TR TB + 12-core SB Mean cores = 16.6	1.89 (1/53) (Hospitalisation for fever)	TR 20-core SB Mean cores = 20	1.92 (1/52) (Hospitalisation for fever)	0.98 (0.06, 15.28)

CI = confidence interval; PIRADS = Prostate imaging reporting and data system; PNB = prior negative biopsy; PSA = prostate specific antigen; SB = systematic biopsy; TB = targeted biopsy; TR = transrectal

**Risk ratio calculated by technical team using tool at https://sample-size.net/risk-ratio/*

2.5 Risk of bias

The results of the risk of bias assessments for the included studies are shown in Table 5.

Table 5. *Risk of bias assessments for included studies of randomised controlled trials studies using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) (Sterne 2019)*

Study	*Source of bias*					*Overall risk of bias*
	Randomisation process	*Deviations from intended interventions*	*Missing outcome data*	*Measurement of the outcome*	*Selection of the reported result*	
Hugosson 2022	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Dadpour 2023	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns

Key to overall rating
Low risk of bias: "Low" for all domains
Some concerns regarding risk of bias: "Some concerns" but not "high" for one or more domains
High risk of bias: "High" for one or more domains

3. GRADE Certainty of the evidence

Hospitalizations within 30 days of biopsy – assessments are shown in Table 6 for PICO 9Ca and Table 7 for PICO 9Cb

Table 6. *GRADE assessment of the certainty of the evidence for the outcome of hospitalisations within 30 days of biopsy from randomised controlled trials comparing targeted biopsy with systematic biopsy with or without targeted biopsy (PICO9Ca).*

GRADE domain	Rating	Reason for rating	Certainty of evidence
Targeted biopsy vs 10-12-core systematic biopsy +/- targeted biopsy			
Risk of bias	No serious concerns	For a single trial reporting this outcome, none of the sources of bias were judged to be at high risk of bias. There were some concerns regarding the risk of bias due to randomisation, deviations from intended interventions and missing outcome data, but these were not considered likely to have caused major distortions to the results for this PICO.	*LOW*
Indirectness	Very serious concerns	In the intervention arm those with a PIRADS of 5 and those with a PSA level ≥ 10 ng/ml underwent a systematic biopsy as well as a targeted biopsy so a systematic biopsy was not entirely eliminated and thus the results were not directly relevant. In addition, a transrectal approach was used and a 10- to 12-core systematic biopsy was performed in the control arm. However, in Australia it is more likely that a transperineal approach, which has a lower risk of infections, will be used, and that over 20 cores will be taken for a systematic biopsy. Consequently, the comparison and its results may not be directly relevant to the Australian context.	
Imprecision	No serious concerns	Based on a risk ratio of 0.29 with 95% confidence interval of 0.03 to 2.57, in a population of 1000 men undergoing biopsy, performing a targeted biopsy only rather a systematic biopsy with or without targeted biopsy is estimated to result in 8 less (11 less, 18 more) hospitalisations within 30 days of biopsy. Using a MCID of 50 hospitalisations within 30 days of biopsy/1000 and thresholds for moderate and large effects of 100 hospitalisations/1000 and 200 hospitalisations/1000, the absolute difference between the two arms was not clinically important, and its 95% CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any relevant trials starting between 2015 and 2019 inclusive with unpublished results.	

CI = confidence interval; MCID = minimal clinically important difference; PIRADS = Prostate Image-Reporting and Data System; PSA = prostate specific antigen

Table 7. *GRADE assessment of the certainty of the evidence for the outcome of hospitalszations within 30 days of biopsy from randomised controlled trial evidence comparing targeted biopsy and < 20-core systematic biopsy with ≥ 20-core systematic biopsy with or without targeted biopsy.*

GRADE domain	*Rating*	*Reason for rating*	*Certainty of evidence*
Targeted biopsy + 12-core systematic biopsy vs 20-core systematic biopsy			
Risk of bias	No serious concerns	For a single trial reporting hospitalisations with fever following biopsy, none of the sources of bias were judged to be at high risk of bias. There were some concerns regarding the risk of bias due to randomisation, deviations from intended interventions, missing outcome data, outcome measurement and selection of reported outcomes arising in many cases from an absence of reported details. None of these sources of bias were considered likely to have caused major distortions to the results for this PICO.	*VERY LOW*
Indirectness	Serious concerns	In this study it is unclear as to how long participants were followed up post biopsy for any hospitalisations or hospitalisations due to biopsy complications. In this study a transrectal approach was used rather than a transperineal approach, the latter of which has a lower risk of infection and is commonly used in Australia. Consequently the outcome may not be directly relevant to the PICO or the Australian context.	
Imprecision	Extremely serious concerns	Based on a risk ratio of 0.98 with 95% confidence interval of 0.06 to 15.28, in a population of 1000 men undergoing biopsy, performing a targeted biopsy and a 12-core systematic biopsy rather than a 20-core biopsy is estimated to result in 0.4 less (18 less, 274 more) hospitalisations for biopsy complications. Using a MCID of 50 hospitalisations within 30 days of biopsy/1000 and thresholds for moderate and large effects of 100 hospitalisations/1000 and 200 hospitalisations/1000, the absolute difference between the two arms was not clinically important, but its 95% CI crossed the thresholds for small, moderate and large increases.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any relevant trials starting between 2015 and 2019 inclusive with unpublished results.	

CI = confidence interval; MCID = minimal clinically important difference

4. Summary of findings

Table 8. *Summary of findings for targeted biopsy vs systematic biopsy with or without targeted biopsy (PICO 9Ca).*

Outcome (MCID)	Time frame	RCTs (N)	Participants (N)	Study results and measurements	Absolute effect estimates				Certainty of evidence (GRADE)	Plain text summary
					Metric	Systematic biopsy +/- targeted biopsy	Targeted biopsy (95% CI)	Difference (95% CI)		
Targeted biopsy vs 10-12-core systematic biopsy +/- targeted biopsy										
Post biopsy hospitalisation (50/1000)	30 days	1	649	RR: 0.29 (0.03, 2.57)	Hospitalisations per 1000	11.5	3.3 (0.3, 29.6)	8 less (11 less, 18 more)	Low[1]	In a population of men undergoing biopsy, undertaking a targeted biopsy only rather than a systematic biopsy as well as a targeted biopsy may result in a clinically **unimportant^** difference in the number of hospitalisations within 30 days of biopsy.

CI = confidence interval; MCID = minimally important difference; RCT = randomised controlled trial; RR = risk ratio
[1] Downgraded by two levels due to very serious concerns re indirectness
^ Using thresholds of 50, 100 and 200 hospitalisations within 30 days of biopsy /1000 for small (minimal clinically important difference), moderate and large effects

Table 9. *Summary of findings for targeted biopsy and < 20-core systematic biopsy vs ≥ 20-core systematic biopsy (PICO 9Cb).*

Outcome (MCID)	Time frame	RCTs (N)	Participants (N)	Study results and measurements	Absolute effect estimates				Certainty of evidence (GRADE)	Plain text summary
					Metric	20-core systematic biopsy	Targeted biopsy + 12-core systematic biopsy (95% CI)	Difference (95% CI)		
Targeted biopsy + 12-core systematic biopsy vs 20-core systematic biopsy										
Hospitalisation for post biopsy fever (50/1000)	NR	1	105	RR: 0.98 (0.06, 15.28)	Hospitalisations per 1000	19.2	18.8 (1.2, 293.4)	0.4 less (18 less, 274 more)	Very low[1]	In a population of men undergoing biopsy, we are uncertain as to whether undertaking a targeted biopsy and a 12-core systematic biopsy rather than a 20-core systematic biopsy will result in a clinically **unimportant^** difference in the number of hospitalisations due to biopsy complications.

CI = confidence interval; MCID = minimally important difference; RCT = randomised controlled trial; RR = risk ratio
[†]Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness
^ Using thresholds of 50, 100 and 200 hospital admissions within 30 days of biopsy /1000 for small (minimal clinically important difference), moderate and large effects

5. Ongoing clinical trials

Two potentially relevant ongoing trial protocols were identified by searches of clinical trial registries or literature searches.

Table 10. *Summary of potentially relevant ongoing randomised controlled trials comparing biopsy protocols with lower numbers of biopsy cores which include a targeted biopsy with a systematic biopsy of ≥ 20 cores with or without MRI-targeted biopsy*

Study ID Publications	Study name, location and study design	Start date	Planned completion date	Population	Intervention	Comparator	Outcomes
NCT04685928	Extended Systematic Versus Mri-Assisted pRostate Transperineal Biopsy (SMART) trial Hong Kong RCT – 2 arms	2021 Recruiting	2025	Biopsy-naïve men aged ≥18 years with clinical suspicion of prostate cancer based on elevated PSA (4-20 ng/mL) +/- abnormal DRE	**TB + 12-core SB** (MRI) If PIRADS score 3-5, transperineal MRI-targeted biopsy (3-4 cores) + 12-core systematic biopsy (sparing MRI targets) If PIRADS score 1-2, no biopsy	**24-core SB** (No mpMRI) Transperineal 24-core systematic biopsy for all men	*Primary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection *Secondary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection of MRI-targeted biopsy only vs systematic biopsy only Clinically insignificant prostate cancer (ISUP Grade 1) detection Biopsies avoided among mpMRI negative men Maximum cancer core length **Adverse events at 30 days post biopsy** Health-related quality of life Cost per diagnosis of cancer

NCT04993508	Randomized Prospective Multi Center Cohort Study for Primary Diagnosis of Clinically Significant Prostate Cancer with Combination of PSA/DRE and Multi Parametric Magnetic Resonance Imaging (PRIMA) Germany RCT – 2 arms	2026 Not yet recruiting	2028	Biopsy-naïve men aged 50 to 75 years with mpMRI PIRADS 4-5, or PIRADS 3 and PSAD > 0.15 ng/mL^2 undergoing prostate biopsy under local or general anaesthesia. mpMRI indication: Elevated PSA (≥4 ng/mL) and/or cancer suspicious DRE	**TB only** Transperineal or transrectal TRUS fusion MRI-targeted biopsy (maximum 6 cores from 3 lesions)	**TB + 12-core SB** Transperineal or transrectal TRUS fusion MRI-targeted biopsy (maximum 6 cores from 3 lesions) + 12-core systematic biopsy	*Primary* Clinically significant prostate cancer (ISUP Grade ≥ 2) detection Clinically insignificant prostate cancer (ISUP Grade 1) detection *Secondary* **Complications rate at 30 days post-biopsy** Number of biopsies avoided Detection rate of MRI in-bore biopsy Detection rate of bpMRI Number of PIRADS upgrades and downgrades Patient-reported outcomes including: Pain score Quality of life

DRE = digital rectal examination; ISUP = International Society of Urological Pathology grade; mpMRI = multiparametric magnetic resonance imaging; PIRADS = Prostate Image-Reporting and Data System; RCT = randomised controlled trial; TRUS = transrectal ultrasound

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APPENDICES

Appendix A: Literature search strategies

A.1 Search strategies for systematic reviews published 2010 onwards

Databases: Medline and Embase databases (via Ovid platform)

#	*Searches*
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2010 -Current"
20	(Systematic* adj3 review*).tw.
21	(meta-analys* or meta analys*).tw.
22	20 or 21
23	19 and 22
24	remove duplicates from 23

Database: Cochrane Database of Systematic Reviews

ID	*Search*
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	prostate
#3	#1 OR #2
#4	MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] explode all trees
#5	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#6	magnetic resonance imaging
#7	mpMRI
#8	MRI
#9	#4 OR #5 OR #6 OR #7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jan 2010 and Jan 2025, in Cochrane Reviews (Word variations have been searched)

A.2 Search strategies for primary studies published 2018 onwards

Databases: Medline, Embase and Cochrane Central Register of Controlled Trials databases (via Ovid platform)

#	Searches
1	*prostate cancer/di [Diagnosis]
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or lesion*)).tw.
3	("clinically significant" and "prostate").tw.
4	1 or 2 or 3
5	multiparametric magnetic resonance imaging/
6	(magnet* adj2 resonance adj2 imag*).tw.
7	"prostate imaging reporting and data system"/
8	(mpMRI or mp-MRI or MRI or PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System").tw.
9	((multiparametric or multi-parametric) adj3 imag*).tw.
10	5 or 6 or 7 or 8 or 9
11	(biops* or prebiopsy or pre-biopsy or patholog* or histopatholog* or histo-patholog*).tw.
12	4 and 10 and 11
13	(((PI-RADS or PIRADS or "Prostate Imaging Reporting and Data System" or multiparametric or multi-parametric or mpMRI or mp-MRI or MRI) adj3 lesion*) and prostat*).tw.
14	11 and 13
15	12 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
21	Randomized Controlled Trial/
22	exp Randomized Controlled Trials as Topic/
23	"Randomized Controlled Trial (topic)"/
24	Controlled Clinical Trial/
25	exp Controlled Clinical Trials as Topic/
26	"Controlled Clinical Trial (topic)"/
27	Randomization/
28	Random Allocation/
29	Double-Blind Method/
30	Double Blind Procedure/
31	Double-Blind Studies/
32	Single-Blind Method/
33	Single Blind Procedure/
34	Single-Blind Studies/
35	Placebos/
36	Placebo/
37	Control Groups/
38	Control Group/
39	(random* or sham or placebo*).ti,ab,hw,kf.
40	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
41	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
42	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
43	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
44	allocated.ti,ab,hw.
45	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
46	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
47	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
48	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
49	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
50	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
51	or/20-50
52	19 and 51
53	remove duplicates from 52

Appendix B: GRADE assessment of the certainty of the evidence

Grade	*Definition*
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix C: Potentially relevant prostate cancer early detection and management guidelines reportedly based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
American Urology Association	https://www.auanet.org/guidelines-and-quality/guidelines/early-detection-of-prostate-cancer-guidelines	Early Detection of Prostate Cancer: AUA/SUO Guideline	2023	The systematic reviews were not accessible

Appendix D: Excluded Studies

Article/Record	*DOI*	*Reason for exclusion*
Articles from primary studies search and citation searching		
Ahlberg 2019	https://dx.doi.org/10.1136/bmjopen-2018-027860	Irrelevant intervention
Alberts 2019	https://dx.doi.org/10.1016/j.eururo.2018.07.031	Excluded study design
Alkema 2022	https://dx.doi.org/10.1016/j.euros.2022.08.005	Excluded study design
Alterbeck 2024	https://dx.doi.org/10.1111/bju.16143	Excluded study design
Amin 2020	https://dx.doi.org/10.1111/bju.14999	Excluded study design
Arsov 2022	https://dx.doi.org/10.1002/ijc.33940	Irrelevant intervention
Auvinen 2024	https://dx.doi.org/10.1001/jama.2024.3841	Irrelevant intervention
Baccaglini 2021	https://dx.doi.org/10.1016/j.clgc.2020.06.008	Excluded study design
Bates 2023	https://doi.org/10.1016/S0302-2838(23)00144-6	Excluded publication type
Bjornebo 2024	https://dx.doi.org/10.1001/jamanetworkopen.2024.7131	Irrelevant intervention
Boschheidgen 2024	https://dx.doi.org/10.1016/j.eururo.2023.09.027	Excluded study design
Bratt 2019	https://dx.doi.org/10.1016/j.eururo.2019.02.035	Irrelevant population
Bryant 2023	https://dx.doi.org/10.1111/bju.15978	Irrelevant comparator
Checcucci 2024	https://doi.org/10.1016/S0302-2838(22)00538-3	Excluded publication type
Checcucci 2023	https://dx.doi.org/10.1177/20514158211023713	Excluded study design
Checcucci 2023	https://doi.org/10.21873/anticanres.16021	Excluded publication type
Checcucci 2022	https://doi.org/10.1097/JU.0000000000002555.11	Excluded publication type
Checcucci 2022	https://doi.org/10.1016/S2666-1683(22)01175-2	Excluded publication type
Chen 2018	https://dx.doi.org/10.1016/j.ajur.2017.07.001	Excluded study design
ChiCTR2000036915 2020	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000036915	Excluded publication type/ Irrelevant comparator
Choi 2019	https://dx.doi.org/10.1016/j.clgc.2018.09.007	Excluded study design
DRKS00032422 2023	https://drks.de/search/en/trial/DRKS00032422	Excluded publication type/ Irrelevant comparator
Eineluoto 2018	https://dx.doi.org/10.1016/j.euo.2018.02.005	Excluded study design
Eklund 2021	https://dx.doi.org/10.1056/NEJMoa2100852	Irrelevant comparator

Elwenspoek 2019	https://dx.doi.org/10.1001/jamanetworkopen.2019.8427	Irrelevant comparator
Emmett 2021	https://dx.doi.org/10.1016/j.eururo.2021.08.002	Excluded study design
Ettala 2022	https://dx.doi.org/10.1136/bmjopen-2021-053118	Irrelevant intervention
Exterkate 2020	https://dx.doi.org/10.1016/j.euo.2019.06.005	Irrelevant outcome
Exterkate 2023	https://dx.doi.org/10.1111/bju.15876	Irrelevant outcome
Fazekas 2024	https://dx.doi.org/10.1001/jamaoncol.2024.0734	Irrelevant comparator
Ghai 2024	https://dx.doi.org/10.1148/radiol.231948	Irrelevant population
Guo 2024	https://dx.doi.org/10.1186/s13244-024-01699-4	Excluded study design
Hamid 2019	https://dx.doi.org/10.1016/j.eururo.2018.08.007	Excluded study design
He 2021	https://dx.doi.org/10.1136/bmjopen-2020-041427	Excluded publication type
Hu 2020	https://dx.doi.org/10.1007/s00261-019-02370-z	Irrelevant comparator
Hugosson 2019	https://doi.org/10.1016/S1569-9056(19)31108-X	Excluded publication type
Israel 2022	https://dx.doi.org/10.1111/bju.15562	Excluded study design
ISRCTN60263108 2022	https://www.isrctn.com/ISRCTN60263108	Excluded publication type/ Irrelevant comparator
Izadpanahi 2021	https://dx.doi.org/10.1038/s41391-021-00366-9	Irrelevant comparator
Jahnen 2024	https://doi.org/10.1016/S0302-2838(24)00876-5	Excluded publication type
Jahnen 2023	https://doi.org/10.1016/S0302-2838(23)00355-X	Excluded publication type
Jiang 2024	https://dx.doi.org/10.1016/j.euo.2023.12.002	Irrelevant comparator
Kasivisvanathan 2018	https://dx.doi.org/10.1056/NEJMoa1801993	Irrelevant comparator
Kasivisvanathan 2019	https://dx.doi.org/10.1016/j.eururo.2019.04.043	Irrelevant comparator
Kasivisvanathan 2022	https://dx.doi.org/10.1371/journal.pone.0263345	Irrelevant comparator
Kelly 2023	https://dx.doi.org/10.1016/j.euros.2023.05.002	Excluded study design
Klotz 2020	https://dx.doi.org/10.1016/j.eururo.2019.10.007	Irrelevant outcome
Klotz 2021	https://dx.doi.org/10.1001/jamaoncol.2020.7589	Irrelevant comparator
Klotz 2022	https://dx.doi.org/10.1016/j.cct.2021.106618	Irrelevant intervention
Klotz 2024	https://dx.doi.org/10.1016/j.euo.2023.09.013	Irrelevant outcome
Kohestani 2021	https://dx.doi.org/10.1080/21681805.2021.1881612	Irrelevant population
Kruger-Stokke 2021	https://dx.doi.org/10.3389/fonc.2021.745657	Irrelevant outcome
Liu 2024	https://dx.doi.org/10.1136/bmjopen-2023-080593	Excluded study design
Luzzago 2021	https://dx.doi.org/10.1038/s41391-020-00290-4	Excluded study design
Mian 2024	https://dx.doi.org/10.1097/JU.0000000000003979	Excluded study design
Moller 2024	https://dx.doi.org/10.1016/j.eururo.2024.01.017	Excluded study design
Morote 2024	https://dx.doi.org/10.3390/cancers16132306	Excluded study design
NCT06303622 2024	https://clinicaltrials.gov/study/NCT06303622	Excluded publication type/ Irrelevant comparator
NCT04953351 2021	https://clinicaltrials.gov/study/NCT04953351	Excluded publication type/ Irrelevant comparator
NCT04993508 2021	https://clinicaltrials.gov/study/NCT04993508	Excluded publication type/ Irrelevant comparator
NCT03572946 2018	https://clinicaltrials.gov/study/NCT03572946	Excluded publication type/ Irrelevant comparator
NCT03632655 2018	https://clinicaltrials.gov/study/NCT03632655	Excluded publication type/ Irrelevant comparator
NICE 2019	https://www.ncbi.nlm.nih.gov/books/NBK576979/	Excluded study design
Nordstrom 2021	https://dx.doi.org/10.1016/S1470-2045%2821%2900348-X	Irrelevant population
Nordstrom 2024	https://dx.doi.org/10.1001/jamanetworkopen.2023.54577	Irrelevant outcome
Panebianco 2018	https://dx.doi.org/10.1016/j.euo.2018.03.008	Irrelevant outcome

Ploussard 2024	https://doi.org/10.1016/j.euo.2024.01.019	Irrelevant intervention
Porpiglia 2023	https://dx.doi.org/10.23736/S2724-6051.22.05189-8	Irrelevant intervention
Porreca 2020	https://dx.doi.org/10.1097/MD.0000000000022059	Irrelevant outcome
Prince 2021	https://dx.doi.org/10.2214/AJR.20.25207	Excluded study design
Rabah 2021	https://dx.doi.org/10.15537/smj.2021.42.6.20200771	Irrelevant comparator
Rai 2021	https://dx.doi.org/10.1016/j.euo.2020.12.012	Irrelevant comparator
Rakauskas 2023	https://dx.doi.org/10.1371/journal.pone.0280262	Excluded study design
Russo 2021	https://dx.doi.org/10.1016/j.euo.2021.03.007	Irrelevant comparator
Saner 2023	https://dx.doi.org/10.1016/j.euo.2022.08.005	Irrelevant outcome
Schiavina 2021	https://dx.doi.org/10.1016/j.urolonc.2020.10.018	Irrelevant comparator
Szewczyk-Bieda 2019	https://dx.doi.org/10.1186/s13063-019-3746-0	Irrelevant comparator
Wagensveld 2021	https://doi.org/10.1016/S0302-2838(21)01279-3	Excluded publication type
Wang 2023	https://dx.doi.org/10.1007/s00345-022-04086-0	Irrelevant population
Wegelin 2019	https://dx.doi.org/10.1016/j.eururo.2018.11.040	No comparative data for outcome
Wegelin 2019	https://dx.doi.org/10.1016/j.euo.2019.08.007	Irrelevant outcome
Wei 2023	https://dx.doi.org/10.1148/radiol.221428	Irrelevant population
Woo 2019	https://dx.doi.org/10.1016/j.euo.2019.05.004	Irrelevant comparator
Yang 2024	https://dx.doi.org/10.1016/j.acra.2024.08.027	Excluded study design
Yusim 2023	https://dx.doi.org/10.1002/pros.24585	Excluded study design
Zhang 2020	https://dx.doi.org/10.4103/jcrt.JCRT_1495_20	Irrelevant intervention
Zhang 2022	https://dx.doi.org/10.3389/fsurg.2022.1058288	Irrelevant intervention
Zhu 2018	https://dx.doi.org/10.7150/jca.24690	Irrelevant comparator
Articles from Haider 2021 and Drost 2019 systematic reviews		
Baco 2016	https://doi.org/10.1016/j.eururo.2015.03.041	Irrelevant comparator
Panebianco 2015	http://dx.doi.org/10.1016/j.urolonc.2014.09.013, 17.e1-7	Irrelevant intervention
Tontilla 2016	https://doi.org/10.1016/j.eururo.2015.05.024	Irrelevant comparator

3.16 Clinical question 10 – Active Surveillance PICO 10A and 10B

Clinical question 10: *What should be the criteria for choosing active surveillance in preference to definitive treatment to offer as primary management to individuals who have a positive prostate biopsy?*

Introduction

For the 2016 guidelines a systematic review was undertaken of randomised controlled trials and non-randomised studies comparing active surveillance with immediate treatment for localised prostate cancer to identify those for whom long term outcomes for active surveillance were comparable to those for immediate treatment. Three cohort studies were included; no randomised controlled trials were found. Given the lack of high quality relevant published evidence, it was decided to complement this systematic review with a systematic review undertaken as part of the UK National Institute for Health and Care Excellence's (NICE) *Clinical Guidelines for Prostate Cancer: Diagnosis and Treatment* (UK National Collaborating Centre for Cancer 2014). This NICE guideline addressed the question: *Which men with localised prostate cancer should be offered active surveillance?*, and used a different approach by assessing prognostic factors for men undergoing active surveillance rather than comparing the effects of different interventions in different groups of men.

Following the publication of the 2016 guidelines the results of the ProtecT trial were published; a randomised controlled trial comparing active surveillance with immediate treatment. Consequently, to address this clinical question for this guideline update the systematic review selection criteria was revised to include only randomised controlled trials of active surveillance compared with immediate treatment for localised prostate cancer.

Systematic review report – Randomised controlled trials comparing active surveillance with immediate definitive treatment for people diagnosed with localised prostate cancer

Authors

Denise Campbell, Isabel Rewais, Chelsea Carle, Rehana Abdus Salam, Susan Yuill, Michael David, Sam Egger, Suzanne Hughes

PICOs

This systematic review addresses the following PICOs which are summarised in detail in Tables 1a and 1b.

PICO 10a: *For individuals with biopsy-diagnosed localised prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than immediate prostatectomy?*

PICO 10b: *For individuals with biopsy-diagnosed localised prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does active surveillance achieve equivalent or better outcomes in terms of length and quality of life than immediate radiotherapy?*

Table 25a. *PICO 10A components*

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Individuals with biopsy-confirmed localised prostate cancer (cT1-2)	Active surveillance	Immediate prostatectomy	All-cause mortality Prostate cancer-specific mortality Metastasis Health-related quality of life Adverse patient-reported outcomes	Randomised controlled trials or systematic reviews thereof

Table 26b. *PICO 10B components*

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Individuals with biopsy- confirmed localised prostate cancer (cT1-2)	Active surveillance	Immediate radiotherapy	All-cause mortality Prostate cancer-specific mortality Metastasis Health-related quality of life Adverse patient-reported outcomes	Randomised controlled trials or systematic reviews thereof

1. Methods

1.1 Revised selection Criteria

Table 27. *Selection criteria for systematic review of randomised controlled trials comparing active surveillance to immediate definitive treatment for individuals diagnosed with localised prostate cancer.*

Selection criteria	***Inclusion criteria***	***Exclusion criteria***
Study type	Intervention	Nomograms (or predictive model) studies
Study design	Randomised controlled trials or systematic reviews thereof	
Population	Individuals with biopsy-confirmed **and** localised (cT1-2) prostate cancer or Subgroups thereof	Studies that restricted participants based on biomarker status More than 10% > cT2 prostate cancer and no subgroup analyses
Intervention	Active surveillance – monitored for disease progression and offered definitive/curative therapy, i.e., prostatectomy or radiotherapy (external beam radiation therapy or brachytherapy) if progression evident	Watchful waiting (men not necessarily offered definitive/curative therapy if disease progresses rather offered treatments to manage symptoms)
Comparator	Immediate definitive/curative treatment: Radical prostatectomy, or External beam radiation therapy, or Brachytherapy	ADT alone Systemic treatment only
Outcome	All-cause mortality Prostate cancer-specific mortality Metastasis (nodal and/or distant) Overall health-related quality of life Adverse patient-reported outcomes: Urinary function/bother Sexual function/bother Bowel function/bother Anxiety Depression	Disease progression
Publication date	1st January 1990 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

ADT = androgen deprivation therapy

1.2 Definitions and terminology

For the purposes of this review:

Localised prostate cancer refers to cancer that is confined within the prostate, classified as clinical stage <T3 (Bruinsma 2017)

Active surveillance is a monitoring strategy for men with localised prostate cancer. It aims to minimise treatment-related toxicity without compromising survival by achieving correct timing for curative treatment for those who may eventually require it.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website

- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e., be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and be published from 2023 onwards so as to include recent published results. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence i.e., did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

This systematic review covers the literature published from January 1990 onwards.

For the 2016 guidelines systematic review, Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 1990 using text terms and, where available, database-specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was coupled with a search for active surveillance and a filter for randomised controlled trials. To identify studies which considered Aboriginal and Torres Strait Islander peoples these searches were then coupled with search terms for Aboriginal and Torres Strait Islander peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

For the 2025 update of this systematic review, assessment of existing guidelines identified a systematic review for the NICE guideline NG131: Prostate cancer: diagnosis and management (NICE 2019) that

adequately captured the relevant literature published from January 1990 to March 2018. We assessed the studies included in this review for inclusion in our systematic review and undertook literature searches to identify randomised controlled trials or systematic reviews thereof published from 2018 onwards. Medline, Embase and Cochrane CENTRAL databases were searched on 28th August 2023 combining text terms and database-specific subject headings for prostate cancer, active surveillance, radical prostatectomy, and radiation therapy, and a filter for randomised controlled trials. Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st September 2024. A complete list of the terms used in the search is included as Appendix A. In addition, the Cochrane Database of Systematic Reviews was searched on 13th March 2024 using the search term "prostate". The searches were designed to identify potentially relevant trials in populations that included Aboriginal and Torres Strait Islander peoples. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

Two reviewers independently extracted data from the included studies (with independent third-reviewer adjudication if needed). The following data was extracted from included studies: Country and year of publication, participant eligibility and age, duration of follow-up, intervention details including the active surveillance monitoring protocol and triggers for change to treatment, comparator details including description of the definitive treatment and any concurrent treatments, participant characteristics for intervention and comparator groups including age, PSA level, Gleason score, ISUP Grade Group and clinical stage, relevant outcomes reported and subgroup data available, and additional information including notable study limitations. The hazard ratio or crude risk ratio and 95% confidence interval for the intention-to-treat analyses were extracted as reported in the study or were calculated using relevant data. Where a study reported definitive treatment as the intervention and active surveillance as the comparator, published hazard ratios and 95% confidence intervals were inverted to reframe active surveillance as the intervention. Crude risk ratios were calculated as the absolute risk (number of events divided by number of participants) per 1000 in the intervention group divided by the absolute risk per 1000 in the comparator group. For patient-reported outcome measures reporting mean scores, mean and standard deviation values were extracted allowing for calculation of the mean difference and 95% confidence interval using an online statistical calculator (MedCalc Software Ltd. 2024). The above effect estimates for relevant subgroups were extracted, if available. Pooled analyses were planned where there were two or more studies reporting the same outcome at corresponding time points. For the summary of finding tables where the effect estimate was a hazard ratio the estimated risk of the outcome in the intervention arm and its 95% confidence interval were calculated using the following formula:

$$1000 \times (1 - S(t)^{HR})$$

where *S(t)* is the estimated probability of no event in the control arm and *HR* is the hazard ratio for the event (Case 2002).

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias of outcomes in each included study (with independent third-reviewer adjudication as needed) using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) (Sterne 2019). The overall risk of bias for each outcome for each study was rated low, some concerns or high for the following sources of bias; the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for each outcome determined to be critical by the Active Surveillance Working Group (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Schunemann 2013) and Schunemann et al 2022, and on guidance for assessing narrative syntheses provided by Murad 2017. For the assessment of risk of bias missing outcome data and measurement of the outcome related to lack of clinician and patient blinding to the group assignment and self-report of the outcome for the patient-reported outcomes were considered important sources of bias.

Imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. For dichotomous outcomes, these thresholds were determined by a reference group consisting of a consumer, a general practitioner, a urology nurse practitioner and clinical specialists following GRADE guidance provided by Schunemann 2022. For continuous patient reported outcomes, based on methods published for individuals diagnosed with localised prostate cancer (Skolarus 2015, Umbehr 2018, Mazariego 2020) and advice from experts, MCIDs were calculated as the half the standard deviation for that outcome of the population at baseline. Where baseline standard deviations were reported only for each arm of a trial, the baseline standard deviation for the entire population was calculated using the formula:

$$s_p = \sqrt{\frac{(n_1 - 1)\, s_1^2 + (n_2 - 1)\, s_2^2}{n_1 + n_2 - 2}}$$

where n_1 = number of participants in arm 1, n_2 = number of participants in arm 2, s_1 = standard deviation for arm 1 and s_2 = standard deviation for arm 2 (Fisher 1970). Imprecision was assessed in the context of whether there was a clinically important increase or decrease. Potential publication bias (or small study effects) was assessed using a Funnel Plot if 10 or more studies. Where there were less than 10 studies clinical trial registries were searched for potentially relevant trials (see Section 1.8 below for search details) that planned report to long term outcomes and commenced before 2007 (with over 15 years of follow-up), and trials that planned to report patient-reported outcomes and commenced before 2017 (with at least 5 years of follow-up), that had not been terminated and for which results had not been published, suggesting publication bias.

The Active Surveillance Working Group determined critical outcomes prior to the assessment of the evidence. Patient-reported outcomes were considered critical at two years; a timepoint where the outcomes would be

impacted by the long-term rather than the short-term effects of immediate treatment, before being affected by aging and the substantial uptake of active treatments amongst those randomised to active surveillance.
As per GRADE guidance, randomised controlled trials started with a high level of certainty in the evidence and were downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.
Definitions of the GRADE ratings of certainty of the overall body of evidence are presented in Appendix B.

1.8 Clinical trial registry searches

Potentially relevant ongoing and unpublished trials were identified from literature and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 16th September 2024 using the search terms listed below.
Clinicaltrials.gov using the terms:

"prostate cancer" and "surveillance"
"prostate cancer" and "active surveillance"

International Clinical Trials Registry Platform (https://trialsearch.who.int/Default.aspx) using the terms:

"active surveillance" and "prostate cancer"
"radical prostatectomy" and "prostate cancer"
"comparative effectiveness" and "surgery" and "prostate cancer"
"comparative effectiveness" and "radiation therapy" and "prostate cancer"
"radiotherapy" and "prostate cancer"
"prostate cancer" and "active monitoring"
"prostate cancer" and "delayed treatment"

2. Results

2.1 Guidelines searches

No relevant guidelines published from 2023 onwards were identified which were reportedly based on systematic reviews of the literature.

2.2 Literature searches

Figure 1 outlines the process of inclusion and exclusion of articles from the 2016 guidelines systematic review and 2025 updated systematic review. For this update, the search of the Cochrane Database of Systematic Reviews did not identify any potentially relevant systematic reviews. The combined search of Medline and Embase retrieved 485 records after removal of duplicates. Titles and abstracts were examined by two reviewers and 26 articles were retrieved for a more detailed evaluation. An additional three potentially relevant articles were identified from the NICE guidelines systematic review (NICE 2019) and reference lists for more detailed evaluation. Two reviewers independently assessed the full texts. The update identified five articles reporting on two randomised controlled trials that met the revised selection criteria and were included; four articles reported on the ProtecT trial and one reported on the PREFERE trial, that met the revised selection

criteria and were eligible for inclusion; no articles from the previous 2016 systematic review met the revised selection criteria. There were no studies that included of Aboriginal and/or Torres Strait Islander peoples that met the selection criteria. The retrieved articles that were not included in the previous review and this review update along with the reasons for their exclusion are documented in Appendices C and D. For the review update the main reasons for exclusion were no comparator of interest and systematic review with different inclusion criteria.

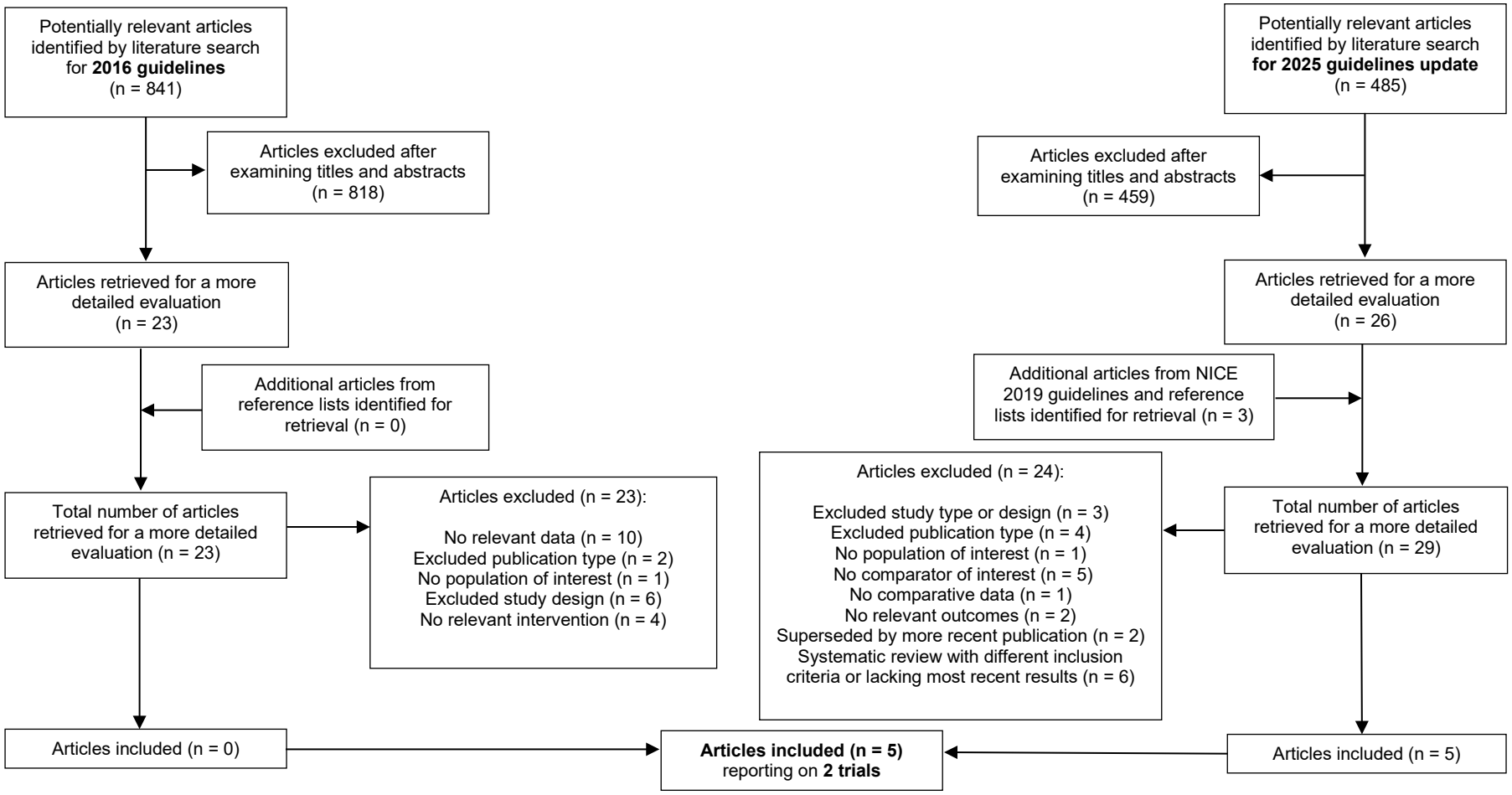

Figure 1. *Process of inclusion and exclusion of published articles from the 2016 guidelines systematic review and 2025 systematic review update*

2.3 Characteristics of included studies

The characteristics of studies included in the systematic review are described in Table 3.

Table 28. *Study characteristics of included randomised controlled trials comparing active surveillances to immediate definitive treatment for men diagnosed with localised prostate cancer.*

Study	*Participants*	*Intervention*	*Comparator: Immediate definitive treatment*	*Outcomes of interest*	*Comments*
ProtecT Trial RCT United Kingdom **Hamdy 2023 & 2016, Donovan 2023 & 2016**	Men aged 50-69 years with a life expectancy ≥10 years contacted via 337 primary care centres in 9 cities and invited to undergo a PSA test in 1999-2009. Eligible men* with a PSA level 3-19.9 ng/ml and histopathological diagnosis of clinically localised prostate cancer (cT1c-T2, NX, M0) on 10-core biopsy were enrolled. Median follow-up: 15 years **N = 1643**	**Active Monitoring –** No confirmatory biopsy <u>Monitoring protocol:</u> PSA monitoring (test every 3 months in year 1, then every 3-6 months). Annual specialist nurse review. Urologist review including DRE if • requested by clinician or patient • disease progression suspected based on: ○ symptomatic disease (urinary or systematic) ○ >20% PSA increase on consecutive measurements, sustained at 3 months ○ ≥50% PSA increase in 12-month period confirmed by repeat tests. <u>Triggers for offering treatment:</u> Disease progression based on restaging and review of PSA patterns, clinical stage and disease grade. Treatment options discussed based on disease grade and clinical stage. Treatment determined by joint clinician-patient decision making. **N = 545** Median age (range): 62 (50-69) years Median PSA (range): 4.6 (3.0-20.9) ng/ml Gleason score ≤6: 77%, 7: 20%	**Radical Prostatectomy** + lymphadenectomy if GS≥7 or PSA ≥10 ng/ml ± adjuvant or salvage radiotherapy (discussed with urologist if positive surgical margins, extracapsular disease, or post-operative PSA level ≥0.2 ng/ml) PSA monitoring (test every 6 months in year 1, then every 6-12 months). **N = 553** Median age (range): 62 (50-69) years Median PSA (range): 4.7 (3.0-18.4) ng/ml Gleason score ≤6: 76%, 7: 22% ISUP Grade Group 1: 77%, 2: 18%, ≥3: 5% Clinical stage T1c: 74%, T2: 26% **External Beam Radiation Therapy** + neoadjuvant and concomitant ADT PSA monitoring (test every 6 months in year 1, then every 12 months). Oncologist review if PSA levels rise by ≥2.0 ng/ml post-nadir or if concerns raised about clinical progression. **N = 545** Median age (range): 62 (49-69) years Median PSA (range): 4.6 (3.0-18.8) ng/ml Gleason score ≤6: 78%, 7: 20% ISUP Grade Group 1: 78%, 2: 15%, ≥3: 7% Clinical stage T1c: 79%, T2: 21%	**Primary outcome:** Prostate cancer-specific mortality **Secondary outcomes:** All-cause mortality Metastatic disease **Patient-reported outcomes:** Urinary function and QoL Sexual function and QoL Bowel function and QoL Overall health-related QoL Anxiety Depression	Study designed to determine the most clinically- and cost-effective method of treating men with clinically localised prostate cancer. In all arms, ADT offered to men if PSA level ≥20 ng/ml, or less if indicated, and skeletal imaging recommended if PSA level ≥10 ng/ml. Details of what constituted disease progression as a trigger for offering definitive treatment were not reported in any of the included articles 488 men underwent RP within 12 months of randomisation (irrespective of allocation): 138/484 (29%) cT1-T2 upstaged to pT3-T4 on RP; 155/483 (32%) ISUP Grade Group upgraded on RP; 133/363 (37%) upgraded from ISUP Grade Group 1 to ≥2 on RP. Metastatic disease included regional node disease

		ISUP Grade Group** 1: 77%, 2: 17%, ≥3: 6% Clinical stage T1c: 75%, T2: 25%			
PREFERE trial RCT **(non-inferiority)** Germany **Wiegel 2021**	Men aged 18-75 years with a life expectancy ≥10 years recruited via 69 study centres from 2012-2016. Eligible men^ with ECOG performance status 0-1, IPSS score <18, PSA a level ≤10 ng/ml and histopathological diagnosis of localised prostate cancer (≤cT2a, NX, M0) with Gleason score ≤7(3+4) were enrolled. **Trial terminated early due to poor patient accrual.** Median follow-up: 19.7 months **N = 345** Age in years: <65: 46%, 65-70: 26%, 71-75: 28% PSA ≤6 ng/ml: 52%, >6 ng/ml: 48% Gleason score ≤6: 65%, 7(3+4): 35%	**Active Surveillance** <u>Monitoring protocol:</u> Confirmatory biopsy at 6 months, re-biopsy after 12 months for GS 6 and after 3 and 12 months for GS 7, then re-biopsy every 3 years up to age 80. Recommended follow-up of PSA test and DRE every 3 months in years 1-2, then every 6 months. <u>Triggers for offering treatment:</u> AS terminated if requested by the patient, or if histological reclassification observed at re-biopsy (ISUP Grade Group** 1 to ≥2, or 2 to ≥3), tumour volume of ISUP Grade Group 2 tumours exceeded ≥ 33% of biopsy cores, or if reclassification to pT3 observed. **N = 130**	**Radical Prostatectomy** + lymphadenectomy if GS 7(3+4) PSA monitoring (schedule NR). **N = 69**	**Patient-reported outcomes (available):** Overall health-related QoL Sexual activity **Primary and secondary outcomes unavailable due to trial termination:** Prostate cancer-specific survival Overall survival Distant metastases	Study designed to assess noninferiority of AS, EBRT, or brachytherapy by PSI to RP for men with low or early intermediate-risk prostate cancer, therefore AS vs EBRT and AS vs PSI not compared. Participants could exclude up to 2 of 4 modalities for randomisation, resulting in 11 different strata within the RCT. All primary biopsies were submitted to reference pathology to obtain a second expert's opinion, prior to randomisation. 114/459 (25%) men who consented to participate were excluded (87/114 due to reference pathology discrepancies). 40 (12%) patients changed from assigned treatment following randomisation.

AS = active surveillance; ADT = androgen deprivation therapy; BPH = benign prostatic hyperplasia; DRE = digital rectal examination; EBRT = external-beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; GS = Gleason Score; IPSS = International Prostate Symptom Score; ISUP = International Society for Urological Pathology; n/a = not available; NR = not reported; PSA = prostate-specific antigen; PSI = permanent seed implantation; QoL = quality of life; RCT = randomised controlled trial; RP = radical prostatectomy

** ProtecT trial exclusion criteria: Men with previous malignancies (except skin cancer), renal transplant or on renal dialysis, major cardiovascular or respiratory comorbidities, bilateral hip replacement or estimated life expectancy of < 10 years were ineligible.*
^ PREFERE trial exclusion criteria: Men with prior treatment for malignancies (except skin cancer and low-risk urothelial cancer), prior surgery for BPH, American Society of Anaesthesiologists (ASA) score 4, proctitis, or use of alpha-blockers or 5-alpha-reductase inhibitors were ineligible. Men with the following contraindications to radiotherapy could be randomised to AS or RP: IPSS >18, residual urine >50 ml, prostate volume >60 ml, predominant middle lobe BPH, inflammatory bowel disease.
*** ISUP Grade Group definitions in Appendix E*

2.4 Results by outcomes of interest

Prostate cancer-specific mortality (median 10 and 15-year follow-up) – results are shown in Section 2.4.1, Table 4

Subgroup analysis of prostate cancer-specific mortality (median 10 and 15-year follow-up) – results are shown in Section 2.4.1, Table 5

All-cause mortality (median 10 and 15-year follow-up) – results are shown in Section 2.4.2, Table 6

Metastatic disease (median 10 and 15-year follow-up) – results are shown in Section 2.4.3, Table 7

Patient-reported outcomes:

Sexual (Section 2.4.4)

- Overall function and quality of life (1, 2, 6, and 12-year follow-up) – results are shown in Table 8
- Bother (1, 2, 6, and 12-year follow-up) – results are shown in Table 9
- Function (1, 2, 6, and 12-year follow-up) – results are shown in Table 10
- Activity (1 and 2-year follow-up) – results are shown in Table 11

Bowel (Section 2.4.5)

- Overall function and quality of life (1, 2, 6, and 12-year follow-up) – results are shown in Table 12
- Bother (1, 2, 6, and 12-year follow-up) – results are shown in Table 13
- Function (1, 2, 6, and 12-year follow-up) – results are shown in Table 14

Urinary (Section 2.4.6)

- Overall function and quality of life (1, 2, 6, and 12-year follow-up) – results are shown in Table 15
- Bother (1, 2, 6, and 12-year follow-up) – results are shown in Table 16
- Function (1, 2, 6, and 12-year follow-up) – results are shown in Table 17

Overall cancer-related quality of life (1, 2, 5 and 10-year follow-up) – results are shown in Section 2.4.7, Table 18

Anxiety (1, 2, 6, and 12-year follow-up) – results are shown in Section 2.4.8, Table 19

Depression (1, 2, 6, and 12-year follow-up) – results are shown in Section 2.4.9, Table 20

2.4.1 Prostate cancer-specific mortality

Table 29. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***prostate cancer-specific mortality^***

Studies (N)	***Follow-up*** *(median)*	***Participants (N)***	***Prostate cancer deaths / person-years (N)***		***Prostate cancer-specific mortality rate*** *per 1000 person-years (95% CI)*		***Hazard ratio*** *(95% CI)*
			Active surveillance	***Definitive treatment***	***Active surveillance***	***Definitive treatment***	
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1098	17 / 7633	12 / 7766	2.2 (1.4, 3.6)	1.5 (0.9, 2.7)	1.52 (0.72, 3.22)*
1 (Hamdy 2016, ProtecT)	10-year	1098	8 / 5393	5 / 5422	1.5 (0.7, 3.0)	0.9 (0.4, 2.2)	Not performed**
Active surveillance *with PSA monitoring vs immediate* ***external beam radiation therapy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1090	17 / 7633	16 / 7628	2.2 (1.4, 3.6)	2.1 (1.3, 3.4)	1.14 (0.57, 2.27)*
1 (Hamdy 2016, ProtecT)	10-year	1090	8 / 5393	4 / 5339	1.5 (0.7, 3.0)	0.7 (0.3, 2.0)	Not performed**

CI = confidence interval; N = number; PSA = prostate-specific antigen
^ Definite or probable prostate cancer mortality, as adjudicated by an independent cause-of-death committee
** Hazard ratios adjusted for trial centre, patient's age at baseline, Gleason score, and PSA level at baseline (log-transformed).*
*** Adjusted analysis not performed due to low number of events.*

Table 30. ***Subgroup analysis*** *results of randomised controlled trials comparing active surveillance with immediate definitive treatment by baseline age, ISUP grade group, PSA level, clinical stage, D'Amico risk score and tumour length for the outcome of* ***prostate cancer-specific mortality***

Studies (N)	***Follow-up*** *(median)*	***Population*** *Subgroup at baseline*	***Participants (N)***	***Active surveillance absolute risk*** *per 1000*	***Definitive treatment absolute risk*** *per 1000*	***Hazard ratio**** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(hazard ratio <1 favours active surveillance)*						
1 (Hamdy 2023, ProtecT)	15-year	Age <65	693	14.7	17.0	0.87 (0.26, 2.86)
1 (Hamdy 2023, ProtecT)	15-year	Age ≥65	405	58.5	30.0	2.13 (0.81,5.88)
1 (Hamdy 2023, ProtecT)	15-year	ISUP Grade Group 1	844	26.3	11.8	2.33 (0.81, 6.67)
1 (Hamdy 2023, ProtecT)	15-year	ISUP Grade Group 2	195	43.0	49.0	0.85 (0.23, 3.13)
1 (Hamdy 2023, ProtecT)	15-year	ISUP Grade Group ≥3	58	60.6	80.0	0.96 (0.13, 6.67)

1 (Hamdy 2023, ProtecT)	15-year	PSA 3.0-5.9 ng/ml	737	35.5	18.9	2.00 (0.79, 5.00)
1 (Hamdy 2023, ProtecT)	15-year	PSA 6.0-9.9 ng/ml	249	32.5	31.7	0.97 (0.24, 3.85)
1 (Hamdy 2023, ProtecT)	15-year	PSA ≥10 ng/ml	112	0	17.9	NA
1 (Hamdy 2023, ProtecT)	15-year	Clinical stage cT1c	820	24.4	14.6	1.72 (1.64, 4.76)
1 (Hamdy 2023, ProtecT)	15-year	Clinical stage cT2	278	51.9	42.0	1.28 (0.43, 3.85)
1 (Hamdy 2023, ProtecT)	15-year	D'Amico risk score Low	671	27.4	11.7	2.27 (0.70, 7.69)
1 (Hamdy 2023, ProtecT)	15-year	D'Amico risk score Intermediate	247	23.3	16.9	1.47 (0.25, 9.09)
1 (Hamdy 2023, ProtecT)	15-year	D'Amico risk score High	103	40.8	111.1	0.38 (0.08, 1.89)
1 (Hamdy 2023, ProtecT)	15-year	Total core tumour length <4mm	442	28.7	12.9	2.33 (0.58, 9.09)
1 (Hamdy 2023, ProtecT)	15-year	Total core tumour length ≥4mm	606	35.0	27.4	1.33 (0.53, 3.33)
1 (Hamdy 2023, ProtecT)	15-year	Max. single core tumour length <2mm	235	18.0	32.3	0.57 (0.10, 3.13)
1 (Hamdy 2023, ProtecT)	15-year	Max. single core tumour length ≥2mm	678	37.4	18.2	2.13 (0.81, 5.56)
Active surveillance *with PSA monitoring vs immediate* ***external beam radiation therapy*** *(hazard ratio <1 favours active surveillance)*						
1 (Hamdy 2023, ProtecT)	15-year	Age <65	681	14.7	29.3	0.49 (0.17, 1.43)
1 (Hamdy 2023, ProtecT)	15-year	Age ≥65	409	58.5	29.4	2.33 (0.87, 6.25)
1 (Hamdy 2023, ProtecT)	15-year	ISUP Grade Group 1	843	26.3	21.2	1.28 (0.53, 3.13)
1 (Hamdy 2023, ProtecT)	15-year	ISUP Grade Group 2	173	43.0	50.0	0.87 (0.22, 3.45)
1 (Hamdy 2023, ProtecT)	15-year	ISUP Grade Group ≥3	74	60.6	73.2	0.85 (0.14, 5.00)
1 (Hamdy 2023, ProtecT)	15-year	PSA 3.0-5.9 ng/ml	737	35.5	27.0	1.41 (0.62, 3.23)
1 (Hamdy 2023, ProtecT)	15-year	PSA 6.0-9.9 ng/ml	240	32.5	51.3	0.58 (0.16, 2.08)
1 (Hamdy 2023, ProtecT)	15-year	PSA ≥10 ng/ml	113	0	0	NA
1 (Hamdy 2023, ProtecT)	15-year	Clinical stage cT1c	839	24.4	23.3	1.10 (0.46, 2.63)
1 (Hamdy 2023, ProtecT)	15-year	Clinical stage cT2	251	51.9	51.7	0.97 (0.33, 2.86)

1 (Hamdy 2023, ProtecT)	15-year	D'Amico risk score Low	671	27.4	17.5	1.59 (0.56, 4.35)
1 (Hamdy 2023, ProtecT)	15-year	D'Amico risk score Intermediate	251	23.3	41.0	0.61 (0.15, 2.56)
1 (Hamdy 2023, ProtecT)	15-year	D'Amico risk score High	93	40.8	0	NA
1 (Hamdy 2023, ProtecT)	15-year	Total core tumour length <4mm	442	28.7	21.5	1.33 (0.41, 4.35)
1 (Hamdy 2023, ProtecT)	15-year	Total core tumour length ≥4mm	603	35.0	34.6	1.06 (0.45, 2.50)
1 (Hamdy 2023, ProtecT)	15-year	Max. single core tumour length <2mm	230	18.0	33.6	0.50 (0.09, 2.70)
1 (Hamdy 2023, ProtecT)	15-year	Max. single core tumour length ≥2mm	677	37.4	27.4	1.45 (0.62, 3.33)

CI = confidence interval; ISUP = International Society for Urological Pathology; max. = maximum; N = number; NA = not available; PSA = prostate-specific antigen
** Hamdy 2023 does not explicitly state baseline characteristics hazard ratio is adjusted for for trial centre, patient's age at baseline, Gleason score, and PSA level at baseline ProtecT trial protocol (Lane 2014) states: "Prespecified subgroup analyses will investigate whether treatment effectiveness in the reduction of prostate cancer-specific mortality is modified by baseline clinical stage, Gleason grade, age, or PSA concentration using stratified analyses for descriptive statistics and by formally including interaction terms in the relevant regression models."*

2.4.2 All-cause mortality

Table 31. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of **all-cause mortality***

Studies (N)	***Follow-up*** *(median)*	***Participants (N)***	***All-cause mortality / person-years (N)***		***All-cause mortality rate*** *per 1000 person-years (95% CI)*		***Hazard ratio**** *(95% CI)*
			Active surveillance	***Definitive treatment***	***Active surveillance***	***Definitive treatment***	
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1098	124 / 7633	117 / 7766	16.2 (13.6, 19.3)	15.0 (12.5, 18.0)	1.12 (0.87, 1.45)
1 (Hamdy 2016, ProtecT)	10-year	1098	59 / 5393	55 / 5422	10.9 (8.5, 14.1)	10.1 (7.8, 13.2)	Not performed**
Active surveillance *with PSA monitoring vs immediate* ***external beam radiation therapy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1090	124 / 7633	115 / 7628	16.2 (13.6, 19.3)	15.0 (12.5, 18.0)	1.14 (0.88, 1.47)
1 (Hamdy 2016, ProtecT)	10-year	1090	59 / 5393	55 / 5339	10.9 (8.5, 14.1)	10.3 (7.9, 13.4)	Not performed**

CI = confidence interval; N = number; PSA = prostate-specific antigen
** Hazard ratios adjusted for trial centre, patient's age at baseline, Gleason score, and PSA level at baseline (log-transformed).*
*** Adjusted analysis not performed due to low number of events.*

2.4.3 Metastatic disease

Table 32. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***metastatic disease^***

Studies (N)	***Follow-up*** *(median)*	***Participants (N)***	***Metastatic disease / person-years (N)***		***Metastatic disease rate*** *per 1000 person-years (95% CI)*		***Hazard ratio**** *(95% CI)*
			Active surveillance	***Definitive treatment***	***Active surveillance***	***Definitive treatment***	
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1098	51 / 7324	26 / 7594	7.1 (5.4, 9.3)	3.5 (2.4, 5.1)	2.13 (1.32, 3.45)
1 (Hamdy 2016, ProtecT)	10-year	1098	33 / 5268	13 / 5377	6.3 (4.5, 8.8)	2.4 (1.4, 4.2)	Not performed**
Active surveillance *with PSA monitoring vs immediate* ***external beam radiation therapy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1090	51 / 7324	27 / 7467	7.1 (5.4, 9.3)	3.7 (2.5, 5.4)	2.08 (1.30, 3.33)
1 (Hamdy 2016, ProtecT)	10-year	1090	33 / 5268	16 / 5286	6.3 (4.5, 8.8)	3.0 (1.9, 4.9)	Not performed**

CI = confidence interval; N = number; PSA = prostate-specific antigen
^ Metastatic disease defined as bony, visceral, or lymph-node metastases confirmed on imaging, or PSA level ≥100 ng/ml.
** Hazard ratios adjusted for trial centre, patient's age at baseline, Gleason score, and PSA level at baseline (log-transformed).*
*** Adjusted analysis not performed due to low number of events.*

2.4.4 Sexual quality of life, bother, and function

Overall sexual function and quality of life

Table 33. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***sexual quality of life: EPIC sexual summary*** *score (range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC sexual summary score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	688	51.6 (27.4)	30.1 (23.2)	21.5 (17.7, 25.3)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	757	48.2 (27.5)	33.4 (23.4)	14.8 (11.2, 18.4)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	891	40.6 (26.7)	32.3 (23.2)	8.3 (5.0, 11.6)

1 (Donovan 2023, ProtecT)	12-year	Overall	495	33.2 (25.2)	30.0 (22.3)	3.2 (-1.0, 7.4)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	681	51.6 (27.4)	43.2 (27.6)	8.4 (4.3, 12.5)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	740	48.2 (27.5)	43.4 (25.2)	4.8 (1.0, 8.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	877	40.6 (26.7)	41.3 (24.9)	-0.7 (-4.1, 2.7)
1 (Donovan 2023, ProtecT)	12-year	Overall	500	33.2 (25.2)	35.2 (22.8)	-2.0 (-6.2, 2.2)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Sexual bother

Table 9. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of **sexual bother: EPIC sexual bother sub-scale score** (range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC sexual bother sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
***Active surveillance** with PSA monitoring vs immediate **radical prostatectomy** (positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	691	67.9 (34.2)	44.6 (34.1)	23.3 (18.2, 28.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	766	62.2 (35.4)	47.0 (33.2)	15.2 (10.3, 20.1)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	882	57.9 (36.6)	51.4 (35.5)	6.5 (1.7, 11.3)
1 (Donovan 2023, ProtecT)	12-year	Overall	494	55.3 (38.5)	54.3 (36.4)	1.0 (-5.6, 7.6)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	682	67.9 (34.2)	57.6 (36.5)	10.3 (5.0, 15.6)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	744	62.2 (35.4)	57.9 (33.5)	4.3 (-0.7, 9.3)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	877	57.9 (36.6)	60.1 (34.9)	-2.2 (-6.9, 2.5)
1 (Donovan 2023, ProtecT)	12-year	Overall	502	55.3 (38.5)	63.5 (37.4)	-8.2 (-14.9, -1.5)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Sexual function - Erections firm enough for intercourse

Table 10. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***sexual function: EPIC item - Erections firm enough for intercourse*** *(at 1, 2, 6 and 12 years). Analysis of population subgroups at baseline are shaded green.*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC item – Erections firm enough for intercourse***		
				Active surveillance *Absolute risk per 1000*	***Definitive treatment*** *Absolute risk per 1000*	***Crude risk ratio*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(crude risk ratio >1 favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	699	494.2	145.7	3.4 (2.6, 4.5)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	770	470.9	191.3	2.5 (2.0, 3.1)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	913	296.5	164.9	1.8 (1.4, 2.3)
1 (Donovan 2023, ProtecT)	12-year	Overall	735	168.5	126.6	1.3 (0.9, 1.9)
1 (Donovan 2023, ProtecT)	12-year	Age <65	489	199.2	154.2	1.3 (0.9, 1.9)
1 (Donovan 2023, ProtecT)	12-year	Age ≥65	246	108.3	71.4	1.5 (0.7, 3.4)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Low	453	204.5	163.1	1.3 (0.8, 1.9)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Intermediate / High	225	129.6	68.4	1.9 (0.8, 4.3)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(crude risk ratio >1 favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	693	494.2	376.1	1.3 (1.1, 1.6)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	766	470.9	340.2	1.4 (1.2, 1.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	908	296.5	274.1	1.1 (0.9, 1.3)
1 (Donovan 2023, ProtecT)	12-year	Overall	723	168.5	147.1	1.1 (0.8, 1.6)
1 (Donovan 2023, ProtecT)	12-year	Age <65	468	199.2	181.0	1.1 (0.8, 1.6)
1 (Donovan 2023, ProtecT)	12-year	Age ≥65	255	108.3	88.9	1.2 (0.6, 2.6)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Low	444	204.5	160.7	1.3 (0.9, 1.9)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Intermediate / High	224	129.6	112.1	1.2 (0.6, 2.3)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen

Sexual activity

***Table 11**. Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of **sexual activity: QLQ-PR25 sexual activity sub-scale score** (range: 0 (most affected) – 100 (least affected) at 1 and 2 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***QLQ-PR25 sexual activity sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
***Active surveillance** with PSA monitoring vs immediate **radical prostatectomy** (positive mean difference favours active surveillance)*						
1 (Weigel 2021, PREFERE)	1-year	Overall	177	54.1 (23.3)	48.8 (21.1)	5.3 (-2.3, 12.9)
1 (Weigel 2021, PREFERE)	2-year	Overall	177	50.9 (38.9)	43.2 (36.4)	7.7 (-5.2, 20.6)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

2.4.5 Bowel quality of life, bother, and function

Overall bowel function and quality of life

Table 12. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of **bowel quality of life: EPIC bowel summary score** (range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC bowel summary score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
***Active surveillance** with PSA monitoring vs immediate **radical prostatectomy** (positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	721	93.4 (8.6)	94.0 (7.7)	-0.6 (-1.8, 0.6)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	800	93.2 (9.4)	93.8 (8.2)	-0.6 (-1.8, 0.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	920	93.0 (9.8)	93.2 (8.7)	-0.2 (-1.4, 1.0)
1 (Donovan 2023, ProtecT)	12-year	Overall	522	92.1 (10.3)	93.1 (8.6)	-1.0 (-2.6, 0.6)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (positive mean difference favours active surveillance)*						

1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	716	93.4 (8.6)	90.5 (12.2)	2.9 (1.4, 4.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	785	93.2 (9.4)	89.3 (12.8)	3.9 (2.3, 5.5)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	923	93.0 (9.8)	91.2 (10.9)	1.8 (0.5, 3.1)
1 (Donovan 2023, ProtecT)	12-year	Overall	526	92.1 (10.3)	90.6 (10.6)	1.5 (-0.3, 3.3)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Bowel bother

Table 13. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***bowel bother: EPIC bowel bother sub-scale score*** *(range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC bowel bother sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	722	94.7 (10.4)	95.2 (9.1)	-0.5 (-1.9, 0.9)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	800	94.2 (11.7)	95.1 (9.4)	-0.9 (-2.4, 0.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	925	93.7 (11.6)	94.2 (10.8)	-0.5 (-1.9, 0.9)
1 (Donovan 2023, ProtecT)	12-year	Overall	522	92.5 (13.2)	94.1 (10.1)	-1.6 (-3.6, 0.4)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	717	94.7 (10.4)	90.7 (14.9)	4.0 (2.1, 5.9)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	789	94.2 (11.7)	89.2 (16.7)	5.0 (3.0, 7.0)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	932	93.7 (11.6)	91.7 (13.7)	2.0 (0.4, 3.6)
1 (Donovan 2023, ProtecT)	12-year	Overall	526	92.5 (13.2)	91.0 (13.5)	1.5 (-0.8, 3.8)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Bowel function - Fecal leakage once per week or more

Table 14. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***bowel function: EPIC item - Fecal leakage once per week or more*** *(at 1, 2, 6 and 12 years). Analysis of population subgroups at baseline are shaded green.*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC item - Fecal leakage once per week or more***		
				Active surveillance *Absolute risk per 1000*	***Definitive treatment*** *Absolute risk per 1000*	***Crude risk ratio*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(crude risk ratio <1 favours active surveillance)*						
1 (Donovan 2023 & 2016, ProtecT)	1-year	Overall	722	27.9	19.2	1.5 (0.6, 3.8)
1 (Donovan 2023 & 2016, ProtecT)	2-year	Overall	802	48.1	36.9	1.3 (0.7, 2.5)
1 (Donovan 2023 & 2016, ProtecT)	6-year	Overall	930	49.8	40.6	1.2 (0.7, 2.2)
1 (Donovan 2023, ProtecT)	12-year	Overall	526	57.0	64.6	0.9 (0.5, 1.7)
1 (Donovan 2023, ProtecT)	12-year	Age <65	345	52.6	69.0	0.8 (0.3, 1.8)
1 (Donovan 2023, ProtecT)	12-year	Age ≥65	181	65.2	56.2	1.2 (0.4, 3.7)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Low	325	73.2	37.3	2.0 (0.8, 5.1)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Intermediate / High	144	27.8	97.2	0.3 (0.1, 1.3)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(crude risk ratio <1 favours active surveillance)*						
1 (Donovan 2023 & 2016, ProtecT)	1-year	Overall	716	27.9	111.7	0.3 (0.1, 0.5)
1 (Donovan 2023 & 2016, ProtecT)	2-year	Overall	788	48.1	99.2	0.5 (0.3, 0.8)
1 (Donovan 2023 & 2016, ProtecT)	6-year	Overall	927	49.8	98.9	0.5 (0.3, 0.8)
1 (Donovan 2023, ProtecT)	12-year	Overall	529	57.0	120.3	0.5 (0.3, 0.9)
1 (Donovan 2023, ProtecT)	12-year	Age <65	336	52.6	121.2	0.4 (0.2, 0.9)
1 (Donovan 2023, ProtecT)	12-year	Age ≥65	193	65.2	118.8	0.5 (0.2, 1.4)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Low	326	73.2	117.3	0.6 (0.3, 1.2)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Intermediate / High	148	27.8	105.3	0.3 (0.1, 1.2)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen

2.4.6 Urinary quality of life, bother, and function

Overall urinary function and quality of life

Table 15. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***urinary quality of life: EPIC urinary summary score*** *(range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC urinary summary score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	721	91.2 (10.1)	86.5 (13.2)	4.7 (3.0, 6.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	794	90.3 (10.9)	88.1 (12.3)	2.2 (0.6, 3.8)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	909	89.0 (12.5)	88.7 (11.3)	0.3 (-1.3, 1.9)
1 (Donovan 2023, ProtecT)	12-year	Overall	518	88.0 (12.8)	87.1 (13.6)	0.9 (-1.4, 3.2)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	715	91.2 (10.1)	91.9 (9.0)	-0.7 (-2.1, 0.7)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	785	90.3 (10.9)	91.4 (9.8)	-1.1 (-2.6, 0.4)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	906	89.0 (12.5)	91.4 (9.2)	-2.4 (-3.8, -1.0)
1 (Donovan 2023, ProtecT)	12-year	Overall	523	88.0 (12.8)	89.5 (10.2)	-1.5 (-3.5, 0.5)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Urinary bother

Table 16. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***urinary bother: EPIC urinary bother sub-scale score*** *(range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC urinary bother sub-scale score***

				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	722	90.0 (12.2)	87.7 (14.1)	2.3 (0.4, 4.2)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	790	88.6 (13.5)	89.0 (13.8)	-0.4 (-2.3, 1.5)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	910	88.0 (13.9)	89.7 (11.9)	-1.7 (-3.4, -0.0)
1 (Donovan 2023, ProtecT)	12-year	Overall	519	86.8 (14.5)	88.6 (14.2)	-1.8 (-4.3, -0.7)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	715	90.0 (12.2)	90.6 (11.0)	-0.6 (-2.3, 1.1)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	781	88.6 (13.5)	90.3 (11.8)	-1.7 (-3.5, 0.1)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	909	88.0 (13.9)	90.3 (11.2)	-2.3 (-3.9, -0.7)
1 (Donovan 2023, ProtecT)	12-year	Overall	524	86.8 (14.5)	88.2 (12.2)	-1.4 (-3.7, 0.9)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Urinary function – Used one or more pads per day in past 4 weeks

Table 17. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***urinary function: EPIC item - One or more pads per day in past 4 weeks*** *(at 1, 2, 6 and 12 years). Analysis of population subgroups at baseline are shaded green.*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC item – One or more pads per day in past 4 weeks***		
				Active surveillance *Absolute risk per 1000*	***Definitive treatment*** *Absolute risk per 1000*	***Crude risk ratio*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(crude risk ratio <1 favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	722	41.8	261.7	0.2 (0.1, 0.3)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	792	38.3	200.0	0.2 (0.1, 0.3)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	908	83.9	173.6	0.5 (0.3, 0.7)
1 (Donovan 2023, ProtecT)	12-year	Overall	754	114.1	235.8	0.5 (0.4, 0.7)

1 (Donovan 2023, ProtecT)	12-year	Age <65	499	111.6	221.8	0.5 (0.3, 0.8)
1 (Donovan 2023, ProtecT)	12-year	Age ≥65	255	119.0	263.6	0.5 (0.3, 0.8)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Low	468	83.7	211.6	0.4 (0.2, 0.6)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Intermediate / High	230	173.9	260.9	0.7 (0.4, 1.1)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (crude risk ratio <1 favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	717	41.8	36.3	1.2 (0.6, 2.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	786	38.3	40.6	0.9 (0.5, 1.9)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	905	83.9	35.4	2.4 (1.3, 4.2)
1 (Donovan 2023, ProtecT)	12-year	Overall	747	114.1	76.5	1.5 (1.0, 2.3)
1 (Donovan 2023, ProtecT)	12-year	Age <65	481	111.6	71.1	1.6 (0.9, 2.8)
1 (Donovan 2023, ProtecT)	12-year	Age ≥65	266	119.0	85.7	1.4 (0.7, 2.9)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Low	459	83.7	56.0	1.5 (0.8, 3.0)
1 (Donovan 2023, ProtecT)	12-year	D'Amico risk score Intermediate / High	234	173.9	117.6	1.5 (0.8, 2.8)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen

2.4.7 Overall cancer-related quality of life

Table 18. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of **cancer-related quality of life: QLQ-C30 global health scale** (range: 0 (most affected) – 100 (least affected) at 1, 2, 5 and 10 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***QLQ-C30 global health scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
***Active surveillance** with PSA monitoring vs immediate **radical prostatectomy** (positive mean difference favours active surveillance)*						
1 (Weigel 2021, PREFERE)	1-year	Overall	177	75.9 (20.2)^	75.6 (21.6)^	0.3 (-6.6, 7.2)
1 (Weigel 2021, PREFERE)	2-year	Overall	177	72.7 (30.3)^	75.2 (30.7)^	-2.5 (-12.7, 7.7)

1 (Donovan **2023** & 2016, ProtecT)	5-year	Overall	781	76.8* (17.6)	78.4 (17.7)	-1.6 (-4.1, 0.9)
1 (Donovan 2023, ProtecT)	10-year	Overall	674	77.2 (17.3)	77.0 (17.5)	0.2 (-2.4, 2.8)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	5-year	Overall	794	76.8 (17.6)	77.4 (19.0)	-0.6 (-3.2, 2.0)
1 (Donovan 2023, ProtecT)	10-year	Overall	675	77.2 (17.3)	76.2 (18.8)	1.0 (-1.7, 3.7)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation
^ calculated by technical team from Figure 4a in Weigel 2021 using tools available at https://www.graphreader.com/

2.4.8 Anxiety

Table 19. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of **anxiety: HADS Anxiety sub-scale score** (range: 0 (least affected) – 21 (most affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***HADS Anxiety sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
***Active surveillance** with PSA monitoring vs immediate **radical prostatectomy** (negative mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	953	4.0 (3.6)	3.6 (3.6)	0.4 (-0.1, 0.9)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	942	3.9 (3.6)	3.6 (3.4)	0.3 (-0.1, 0.7)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	923	4.1 (3.9)	3.7 (3.5)	0.4 (-0.1, 0.9)
1 (Donovan 2023, ProtecT)	12-year	Overall	507	3.7 (3.5)	3.6 (3.5)	0.1 (-0.5, 0.7)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (negative mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	951	4.0 (3.6)	3.7 (3.6)	0.3 (-0.2, 0.8)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	937	3.9 (3.6)	3.7 (3.4)	0.2 (-0.2, 0.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	923	4.1 (3.9)	3.4 (3.2)	0.7 (0.2, 1.2)
1 (Donovan 2023, ProtecT)	12-year	Overall	516	3.7 (3.5)	4.0 (3.7)	-0.3 (-0.9, 0.3)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

2.4.9 Depression

Table 20. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***Depression sub-scale score*** *(range: 0 (least affected) – 21 (most affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***HADs depression sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(negative mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	958	2.4 (2.9)	2.4 (2.9)	0.0 (-0.4, 0.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	953	2.6 (3.0)	2.5 (2.7)	0.1 (-0.3, 0.5)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	923	3.1 (3.4)	2.7 (3.1)	0.4 (0.0, 0.8)
1 (Donovan 2023, ProtecT)	12-year	Overall	505	3.1 (3.3)	3.0 (3.2)	0.1 (-0.5, 0.7)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(negative mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	952	2.4 (2.9)	2.5 (2.7)	-0.1 (-0.5, 0.3)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	943	2.6 (3.0)	2.6 (2.9)	0.0 (-0.4, 0.4)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	928	3.1 (3.4)	2.7 (2.9)	0.4 (0.0, 0.8)
1 (Donovan 2023, ProtecT)	12-year	Overall	513	3.1 (3.3)	3.6 (3.5)	-0.5 (-1.1, 0.1)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

2.5 Risk of bias

The results of the risk of bias assessments for the included randomised controlled trials are shown in Figure 2.

Risk of Bias Assessment for the ProtecT Trial Outcomes						
Outcomes	D1	D2	D3	D4	D5	Overall
Prostate cancer specific mortality at 15-year follow-up	+	+	+	+	+	+
Prostate cancer specific mortality at 10-year follow-up	+	+	+	+	+	+
All-cause mortality at 15-year follow-up	+	+	+	+	+	+
All-cause mortality at 10-year follow-up	+	+	+	+	+	+
Metastatic disease at 15-year follow-up	+	+	+	+	+	+
Metastatic disease at 10-year follow-up	+	+	+	+	+	+
Sexual quality of life: EPIC sexual summary score						
At 1 year	+	+	!	!	!	!
At 2 years	+	+	!	!	!	!
At 6 years	+	+	+	!	!	!
At 12 years	+	+	-	!	!	-
Sexual quality of life: EPIC sexual bother subscale						
At 1 year	+	+	!	!	!	!
At 2 years	+	+	!	!	!	!
At 6 years	+	+	+	!	!	!
At 12 years	+	+	-	!	!	-
Sexual quality of life: EPIC item erection firm enough for intercourse						
At 1 year	+	+	!	!	!	!
At 2 years	+	+	!	!	!	!
At 6 years	+	+	+	!	!	!
At 12 years	+	+	-	!	!	-
Bowel function and quality of life: EPIC bowel summary score						
At 1 year	!	+	!	!	!	!
At 2 years	!	+	!	!	!	!
At 6 years	!	+	+	!	!	!
At 12 years	!	+	-	!	!	-
Bowel function and quality of life: EPIC bowel bother sub-scale score						
At 1 year	!	+	!	!	!	!
At 2 years	!	+	!	!	!	!
At 6 years	!	+	+	!	!	!
At 12 years	!	+	-	!	!	-
Bowel function and quality of life: Fecal leakage once per week or more						
At 1 year	!	+	!	+	!	!
At 2 years	!	+	!	+	!	!
At 6 years	!	+	+	+	!	!
At 12 years	!	+	-	+	!	-
Urinary function and quality of life: EPIC urinary summary score						
At 1 year	+	+	!	!	!	!
At 2 years	+	+	!	!	!	!
At 6 years	+	+	+	!	!	!
At 12 years	+	+	-	!	!	-
Urinary function and quality of life: EPIC urinary bother sub-scale score						
At 1 year	+	+	!	!	!	!
At 2 years	+	+	!	!	!	!
At 6 years	+	+	+	!	!	!
At 12 years	+	+	-	!	!	-
Urinary function and quality of life: one or more pad per day						
At 1 year	+	+	!	+	!	!
At 2 years	+	+	!	+	!	!
At 6 years	+	+	+	+	!	!
At 12 years	+	+	-	+	!	-
Cancer-related quality of life: QLQ-C30 global health scale						
At 5 years	+	+	-	!	!	-
At 10 years	+	+	-	!	!	-
HADS Anxiety sub-scale score						
At 1 year	+	+	+	!	!	!
At 2 years	+	+	+	!	!	!
At 6 years	+	+	+	!	!	!
At 12 years	+	+	-	!	!	-
HADS Depression sub-scale score						
At 1 year	+	+	+	!	!	!
At 2 years	+	+	+	!	!	!
At 6 years	+	+	+	!	!	!
At 12 years	+	+	-	!	!	-
Risk of Bias Assessment for the PREFERE Trial Outcomes						
Sexual activity: QLQ-PR25 sexual activity sub-scale score	-	-	-	!	-	-
Cancer-related quality of life: QLQ-C30 global health scale	-	-	-	!	-	-

+	Low Risk
!	Some Concerns
-	High Risk
D1	Randomisation Process
D2	Deviations from the Intended Intervention
D3	Missing Outcome Data
D4	Measurement of the Outcome
D5	Selection of Reported Results

Figure 2. *Risk of bias assessments for included randomised controlled trials using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) (Sterne 2019)*

Key to overall rating
Low risk of bias: "Low" for all domains
Some concerns regarding risk of bias: "Some concerns" but not "high" one or more domains
High risk of bias: "High" for one or more domains

3. GRADE assessment of the certainty of the evidence

Results for 56 important outcomes were extracted. Of these outcomes, 11 were considered critical by the Active Surveillance Working Group. Assessments of the certainty of the evidence for each critical outcome are shown in the tables below.

Prostate cancer-specific mortality (median 15-year follow-up) – assessments are shown in Table 21

All-cause mortality (median 15-year follow-up) – assessments are shown in Table 22

Metastatic disease (median 15-year follow-up) – assessments are shown in Table 23

Sexual quality of life (2-year follow-up) – assessments are shown in Table 24

Sexual bother (2-year follow-up) – assessments are shown in Table 25

Bowel quality of life (2-year follow-up) – assessments are shown in Table 26

Bowel bother (2-year follow-up) – assessments are shown in Table 27

Urinary quality of life (2-year follow-up) – assessments are shown in Table 28

Urinary bother (2-year follow-up) – assessments are shown in Table 29

Overall / cancer-related quality of life (2-year follow-up) – assessments are shown in Table 30

Anxiety (2-year follow-up) – assessments are shown in Table 31

Table 21. *GRADE assessment of the certainty of the evidence for the outcome of* ***prostate cancer-specific mortality (median 15-year follow-up)*** *from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy***			
Risk of bias	No serious concerns ***Subgroup analyses*** *Age* No serious concerns *D'Amico risk score* Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, outcome was ascertained by trained researchers after reviewing medical records of deceased participants, anonymised, and then reviewed by an independent endpoint committee who were masked to trial assignments. Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable. ***Subgroup analyses*** Randomisation unlikely to be impacted for age subgroup analyses as age was a minimisation variable. D'Amico risk score was not a minimisation variable so increased risk that those in intervention differ from those in control group.	***VERY LOW*** ***Subgroup analyses*** *Age < 65 years* *Age ≥ 65 years* *Low D'Amico risk score* *Intermediate D'Amico risk score* *High D'Amico risk score* ***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Very serious concerns ***Subgroup analyses*** *Age < 65 years* *Age ≥ 65 years* Very serious concerns *Low D'Amico risk score* Very serious concerns *Moderate and high D'Amico risk scores* Extremely serious concerns	Based on a hazard ratio of 1.52 with 95% confidence interval of 0.72 to 3.22, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 11 more (6 fewer to 47 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was not clinically important, and the 95%CI crossed thresholds for a clinically important increase (small) and for a moderate increase. ***Subgroup analyses*** *For subgroup aged < 65 years* in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 2 fewer (13 fewer to 31 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was not clinically important, and the 95%CI crossed the thresholds for clinically important (small) and moderate increases. *For subgroup aged ≥ 65 years* in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 33 more (6 fewer to 134 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was clinically important (moderate increase), and the 95%CI crossed thresholds for no change and for a clinically unimportant increase as well as a large increase. *For subgroup with low D'Amico risk score* in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 15 more (4 fewer to 75 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was clinically important, but the 95%CI crossed thresholds for no change and clinically important, moderate and large increases.	

		For subgroup with intermediate D'Amico risk score in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 8 more (13 less, 127 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was not clinically important the 95%CI crossed thresholds for a clinically important (small) increase and moderate and large increases. *For subgroup with high D'Amico risk score* in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 67 fewer (102 fewer to 89 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was clinically important (large decrease), but the 95%CI crossed thresholds for moderate and small clinically important decreases and clinically important (small), moderate and large increases.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	No serious concerns ***Subgroup analyses*** *Age* No serious concerns *D'Amico risk score* Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, outcome was ascertained by trained researchers after reviewing medical records of deceased participants, anonymised, and then reviewed by an independent endpoint committee who were masked to trial assignments. Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable. ***Subgroup analyses*** Randomisation unlikely to be impacted for age subgroup analyses as age was a minimisation variable. D'Amico risk score was not a minimisation variable so increased risk that those in intervention differ from those in control group.	***VERY LOW*** ***Subgroup analyses*** *Age < 65 years* *Age ≥ 65 years* *Low D'Amico risk score* *Moderate D'Amico risk score* ***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Very serious concerns ***Subgroup analyses*** *Age < 65 years* *Age ≥ 65 years* Very serious concerns *Low D'Amico risk score* Very serious concerns *Moderate D'Amico risk score* Extremely serious concerns	Based on a hazard ratio of 1.14 with 95% confidence interval of 0.57 to 2.72, in a population of 1000 men with localised prostate cancer undergoing active surveillance, using PSA testing only rather than radiotherapy is estimated to result in 4 more (13 fewer to 36 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was not clinically important, and the 95%CI crossed thresholds for a small clinically important increase and for a moderate increase. ***Subgroup analyses*** *For subgroup aged < 65 years* in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than radiotherapy is estimated to result in 15 fewer (24 fewer to 12 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000 the 95%CI crossed the threshold for a clinically important decrease and no effect. *For subgroup aged ≥ 65 years* in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than radiotherapy is estimated to result in 38 more (4 fewer to 141 more) prostate cancer deaths at 15 years follow-up.	

		Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was clinically important (moderate increase), but the 95%CI crossed thresholds for no change, and a clinically unimportant increase, as well as a large increase. *For subgroup with low D'Amico risk score* in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than radiotherapy is estimated to result in 10 more (8 fewer to 56 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was not clinically important, and the 95%CI crossed thresholds for a small clinically important increase and for a moderate increase. *For subgroup with intermediate D'Amico risk score* in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than radiotherapy is estimated to result in 16 less (35 less, 61 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was clinically important (moderate decrease), but the 95%CI crossed thresholds for a small decrease and clinically important, moderate and large increases. *Not assessable for subgroup with high D'Amico risk score* as Hazard ratio was not calculable.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 22. *GRADE assessment of the certainty of the evidence for the outcome of **all-cause mortality (median 15-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, outcome was ascertained by reviewing death certificate. Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Extremely serious concerns	Based on a hazard ratio of 1.12 with 95% confidence interval of 0.87 to 1.45, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 22 more (25 fewer to 80 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was clinically important (small increase), but the 95%CI crossed the thresholds for a clinically important small decrease, no change and a clinical unimportant increase as well as moderate and large increases.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	

Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials with planned completion dates before 2023 that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, outcome was ascertained by reviewing death certificate. Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Extremely serious concerns	Based on a hazard ratio of 1.14 with 95% confidence interval of 0.88 to 1.47, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than radiotherapy is estimated to result in 26 more (23 fewer to 83 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was clinically important (small increase), but the 95%CI crossed the thresholds for a small decrease, no difference and a clinically unimportant increase as well as moderate and large increases.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 23. *GRADE assessment of the certainty of the evidence for the outcome of **metastatic disease (median 15-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, metastases were confirmed on imaging or a PSA level of ≥100 ng/mL (considered objective outcomes in this context). Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a hazard ratio of 2.13 with 95% confidence interval of 1.32 to 3.45, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is	

		estimated to result in 51 more (15 to 106 more) men diagnosed with metastatic prostate cancer at 15 years follow-up. Using a MCID of 30 diagnoses of metastatic disease /1000 at 15 years of follow-up and thresholds for moderate and large effects of 60/1000 and 120/1000, the effect estimate was clinically important (moderate increase), but the 95%CI crossed the threshold for a clinically important small increase/clinically unimportant increase.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, metastases were confirmed on imaging or a PSA level of ≥100 ng/mL (considered objective outcomes in this context). Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a hazard ratio of 2.08 with 95% confidence interval of 1.30 to 3.33, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than radiotherapy is estimated to result in 51 more (14 to 106 more) men diagnosed with metastatic prostate cancer at 15 years follow-up. Using a MCID of 30 diagnoses of metastatic disease /1000 at 15 years of follow-up and thresholds for moderate and large effects of 60/1000 and 120/1000, the effect estimate was clinically important (moderate increase), but the 95%CI crossed the threshold for a clinically important small increase/clinically unimportant increase.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 24. *GRADE assessment of the certainty of the evidence for the outcome of **sexual quality of life (EPIC sexual summary score at 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 69% of the participants with 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline	***VERY LOW***

		measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a mean increase in score of 14.8 with 95% confidence interval of 11.2 to 18.3 and using a MCID of a mean difference of 11.6 and mean difference thresholds for moderate and large effects of 23.2 and 46.4, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 69% of the participants with 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean increase in score of 4.8 with 95% confidence interval of 1.0 to 8.6 and using a MCID of a mean difference of 11.6 and mean difference thresholds for moderate and large effects of 23.2 and 46.4, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 25. *GRADE assessment of the certainty of the evidence for the outcome of **sexual bother (EPIC sexual bother subscale at 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 69% of the participants with 2-year follow-up. The clinicians and patients were unblinded to the group assignment	***VERY LOW***

		and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a mean increase in score of 15.2 with 95% confidence interval of 10.3 to 20.1 and using a MCID of a mean difference of 14.8 and mean difference thresholds for moderate and large effects of 29.6 and 59.2, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 69% of the participants with 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean increase in score of 4.3 with 95% confidence interval of 0.7 less to 9.3 more and using a MCID of a mean difference of 14.8 and mean difference thresholds for moderate and large effects of 29.6 and 59.2, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 26. *GRADE assessment of the certainty of the evidence for the outcome of **bowel quality of life (EPIC bowel summary score at 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, there were some concerns with the process of randomisation due to baseline differences between the three study groups. The outcome measure was added during the trial and hence	***LOW***

		baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean decrease in score of 0.6 with 95% confidence interval of 1.8 less to 0.6 more and using a MCID of a mean difference of 4.1 and mean difference thresholds for moderate and large effects of 8.2 and 16.4, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance *with PSA monitoring vs immediate* ***EBRT***			
Risk of bias	Serious concerns	For a single trial reporting this outcome, there were some concerns with the process of randomisation due to baseline differences between the three study groups. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	*For 2-year follow-up*: Single trial reporting a mean difference of 3.9 with 95% confidence interval of 2.3 to 5.5. Imprecision was rated to be a serious concern due to the lack of clinically important change in the outcome. Based on a mean increase in score of 3.9 with 95% confidence interval of 2.3 to 5.5 and using a MCID of a mean difference of 4.1 and mean difference thresholds for moderate and large effects of 8.2 and 16.4, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 27. *GRADE assessment of the certainty of the evidence for the outcome of* ***bowel bother (EPIC bowel bother sub-scale score at 2-year follow-up)*** *from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***

Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, there were some concerns with the process of randomisation due to baseline differences between the three study groups. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 73% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean decrease in score of 0.9 with 95% confidence interval of 2.4 less to 0.6 more and using a MCID of a mean difference of 4.9 and mean difference thresholds for moderate and large effects of 9.8 and 19.6, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	Serious concerns	For a single trial reporting this outcome, there were some concerns with the process of randomisation due to baseline differences between the three study groups. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 73% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a mean increase in score of 5.0 with 95% confidence interval of 3.0 to 7.0 and using a MCID of a mean difference of 4.9 and mean difference thresholds for moderate and large effects of 9.8 and 19.6, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 28. *GRADE assessment of the certainty of the evidence for the outcome of **urinary quality of life (EPIC urinary summary score at 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	Rating	Reason for rating	Certainty of evidence
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean increase in score of 2.2 with 95% confidence interval of 0.6 to 3.8 and using a MCID of a mean difference of 4.5 and mean difference thresholds for moderate and large effects of 9.0 and 18.0, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	*For 2-year follow-up:* Single trial reporting a mean difference of -1.1 with 95% confidence interval of -2.6 to 0.4. Imprecision was rated to be a serious concern as the confidence interval crosses the null effect (0). Based on a mean decrease in score of 1.1 with 95% confidence interval of 2.6 less to 0.4 more and using a MCID of a mean difference of 4.5 and mean difference thresholds for moderate and large effects of 9.0 and 18.0, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 29. *GRADE assessment of the certainty of the evidence for the outcome of **urinary bother (EPIC urinary bother sub-score at 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	*Rating*	*Reason for rating*	*Certainty of evidence*
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean decrease in score of 0.4 with 95% confidence interval of 2.3 less to 1.5 more and using a MCID of a mean difference of 5.8 and mean difference thresholds for moderate and large effects of 11.6 and 23.2, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean decrease in score of 1.7 with 95% confidence interval of 3.5 less to 0.1 more and using a MCID of a mean difference of 5.8 and mean difference thresholds for moderate and large effects of 11.6 and 23.2, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 30. *GRADE assessment of the certainty of the evidence for the outcome of **cancer-related quality of life (QLQ-C30 score at 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be high for the process of randomisation as patients could exclude up to two choices from four possible study arms. There was no information provided on methods of randomisation and allocation concealment. Baseline differences between the trial arms were not reported as the trial was prematurely closed due to poor recruitment. The risk of bias due to deviations from intended interventions, missing outcome data and selection of reported results were also judged to be high as the trial was prematurely closed due to poor recruitment.	***LOW***
Indirectness	No serious concerns	The population, intervention, comparator and outcomes of this trial were relevant.	
Imprecision	Serious concerns	Based on a mean decrease in score of 2.5 with 95% confidence interval of 12.7 less to 7.7 more and using a MCID of a mean difference of 11.6 and mean difference thresholds for moderate and large effects of 23.2 and 46.4, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 31. *GRADE assessment of the certainty of the evidence for the outcome of **anxiety (HADS anxiety sub score 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The follow-up was complete for 86% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean increase in score of 0.3 with 95% confidence interval of 0.1 less to 0.8 more and using a MCID of a mean difference of 1.7 and mean difference thresholds for moderate and large effects of 3.4 and 6.8, the 95%CI did not cross any thresholds.	

Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	
Active surveillance *with PSA monitoring vs immediate* ***EBRT***			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The follow-up was complete for 86% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean increase in score of 0.2 with 95% confidence interval of 0.2 less to 0.6 more and using a MCID of a mean difference of 1.7 and mean difference thresholds for moderate and large effects of 3.4 and 6.8, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

4. Summary of findings

Table 32. *Summary of findings for active surveillance vs immediate prostatectomy (PICO10a)*

Outcome (MCID)	*Time frame (years)*	*RCTs (N)*	*Participants (N)*	*Study results and measurements*	*Absolute effect estimates*				*Certainty of evidence (GRADE)*	*Plain text summary*
					Metric	*Immediate prostatectomy*	*Active surveillance (95% CI)*	*Difference (95% CI)*		
Active surveillance based only on PSA monitoring										
Prostate cancer-specific deaths (15/1000)	15 (median)	1	1098	HR: 1.52 (0.72, 3.22)	Prostate cancer deaths per 1000	21.7	32.8 (15.7, 68.2)	11 more per 1000 (6 fewer, 47 more)	Very low[3]	We are uncertain as to whether active surveillance results in a clinically **unimportant^** increase in prostate cancer mortality when compared with immediate prostatectomy.
All-cause deaths (15/1000)	15 (median)	1	1098	HR: 1.12 (0.87, 1.45)	Deaths due to any cause per 1000	211.6	233.8 (186.9, 291.6)	22 more (25 fewer, 80 more)	Very low[2]	We are uncertain as to whether active surveillance results in a clinically **important (small)^** increase in mortality when compared with immediate prostatectomy.
Metastatic disease (30/1000)	15 (median)	1	1098	HR: 2.13 (1.32, 3.45)	Metastatic disease per 1000	47.0	97.5 (61.6, 153.0)	51 more (15 more, 106 more)	Low[1]	Active surveillance may result in a clinically **important (small)^^** increase in metastatic prostate cancer diagnoses when compared with immediate prostatectomy.
Sexual quality of life (11.6)*	2	1	757	Measured by: EPIC sexual summary score Scale: 0-100 Higher better	Mean EPIC sexual summary score	33.4 (mean)	49.2 (mean) (44.6, 51.8)	MD: 14.8 more (11.2 more, 18.4 more)	Very low[4]	We are uncertain as to whether active surveillance results in a clinically **important (small)*^** increase sexual quality of life when compared with immediate prostatectomy
Sexual bother (14.8)*	2	1	766	Measured by: EPIC sexual bother score Scale: 0-100 Higher better	Mean EPIC sexual bother score	47.0 (mean)	62.2 (mean) (57.0, 67.1)	MD: 15.2 more (10.3 more, 20.1 more)	Very low[4]	We are uncertain as to whether active surveillance results in a **clinically important (small)*^** decrease in sexual bother when compared with prostatectomy
Bowel quality of life (4.1)*	2	1	800	Measured by: EPIC bowel summary score Scale: 0-100 Higher better	Mean EPIC bowel summary score	93.8 (mean)	93.2 (mean) (92.0, 94.4)	MD: 0.6 less (1.8 less, 0.6 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in bowel quality of life when compared with immediate prostatectomy
Bowel bother (4.9)*	2	1	800	Measured by: EPIC bowel	Mean EPIC bowel bother	95.1 (mean)	94.2 (mean) (92.7, 95.7)	MD: -0.9 less	Low[5]	Active surveillance may result in a clinically **unimportant*^**

				bother score Scale: 0-100 Higher better	sub-scale score			(2.4 less, 0.6 more)		difference in bowel bother when compared with immediate prostatectomy
Urinary quality of life (4.5)*	2	1	794	Measured by: EPIC urinary summary score Scale: 0-100 Higher better	Mean EPIC urinary summary score	88.1 (mean)	90.3 (mean) (88.7, 91.9)	MD: 2.2 more (0.6 more, 3.8 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in urinary quality of life when compared with immediate prostatectomy
Urinary bother (5.8)*	2	1	790	Measured by: EPIC urinary bother score Scale: 0-100 Higher better	Mean EPIC urinary bother sub-score	89.0 (mean)	88.6 (mean) (86.7, 90.5)	MD: 0.4 less (2.3 less, 1.5 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in urinary bother when compared with immediate prostatectomy
Anxiety (1.7)*	2	1	942	Measured by: HADS anxiety sub score Scale: 0-21 Lower better	Mean HADS anxiety sub score	3.6 (mean)	3.9 (mean) (3.5, 4.4)	MD: 0.3 more (0.1 less, 0.8 more)	Low[5]	Active may result in a clinically **unimportant*^** difference in anxiety when compared with immediate prostatectomy
Active surveillance included biopsies at 6 months, 12 months and then every 3 years										
Cancer-related quality of life (11.6)**	2	1	177	Measured by: QLQ-C30 score Scale: 0-100 Higher better	Mean QLQ-C30 score	75.3 (mean)	72.8 (mean) (62.6, 83.0)	MD: 2.5 less (12.7 less, 7.7 more)	Low[6]	Active surveillance may result in a clinically **unimportant*^** difference in cancer-related quality of life when compared with immediate prostatectomy

CI = confidence interval; HADS = hospital anxiety and depression scale; HR = hazard ratio; MCID = minimally important difference; MD = mean difference; N = number; PSA = prostate specific antigen; RCT = randomised controlled trial

** Half the standard deviation of the **baseline** scores for the study for which results reported (Protect Trial)*

*** Half the standard deviation of the **baseline** scores estimated using GraphReader from Figure 4a in Weigel 2021, the study for which results reported*

[1] Downgraded by two levels due to serious concerns re: imprecision and indirectness

[2] Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness

[3] Downgraded by three levels due to very serious concerns re imprecision and serious concerns re indirectness

[4] Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision

[5] Downgraded by two levels due to serious concerns re risk of bias and indirectness

[6] Downgraded by two levels due to serious concerns re risk of bias and imprecision

^ Using thresholds of 15, 30 and 60 deaths /1000 for small (minimal clinically important difference), moderate and large effects

^^ Using thresholds of 30, 60 and 120 metastatic disease diagnoses /1000 for small (minimal clinically important difference), moderate and large effects

**^ Using thresholds of MCID (half standard deviation of baseline score), 2 x MCID and 4 x MCID for small (minimal clinically important difference), moderate and large effects*

Table 33. *Summary of findings for active surveillance based only on PSA monitoring vs immediate prostatectomy by age and D'Amico risk score subgroups (PICO10a)*

Outcome (MCID)	*Time frame (years)*	*RCTs (N)*	*Participants (N)*	*Subgroup*	*Study results*	*Absolute effect estimates*				*Certainty of evidence (GRADE)*	*Plain text summary*
						Metric	*Immediate prostatectomy*	*Active surveillance (95% CI)*	*Difference (95% CI)*		
Prostate cancer-specific deaths (15/1000)	15 (median)	1	1098	Age < 65 years N = 693	HR: 0.87 (0.26, 2.86)	Prostate cancer deaths per 1000	17.0	14.8 (4.4, 47.9)	2 fewer (13 fewer, 31 more)	Very low[3]	For men aged < 65 years we are uncertain as to whether active surveillance results in a clinically **unimportant^** change in prostate cancer mortality when compared with immediate prostatectomy
				Age ≥ 65 years N = 405	HR: 2.13 (0.81, 5.88)	Prostate cancer deaths per 1000	30.0	62.8 (24.4, 164.0)	33 more (6 fewer, 134 more)	Very low[3]	For men aged ≥ 65 years we are uncertain as to whether active surveillance results in a clinically **important (moderate)^** increase in prostate cancer mortality when compared with immediate prostatectomy
	15 (median)	1	1021	D'Amico risk score Low N = 671	HR: 2.27 (0.70, 7.69)	Prostate cancer deaths per 1000	11.7	26.4 (8.2, 86.5)	15 more (4 fewer, 75 more)	Very low[1]	For men with a low D'Amico risk score we are uncertain as to whether active surveillance results in a clinically **important (small)^** increase in prostate cancer mortality when compared with immediate prostatectomy
				D'Amico risk score Intermediate N = 247	HR: 1.47 (0.25, 9.09)	Prostate cancer deaths per 1000	16.9	24.7 (4.3, 143.5)	8 more (13 fewer, 127 more)	Very low[2]	For men with an intermediate D'Amico risk score we are uncertain as to whether active surveillance results in a clinically **unimportant^** increase in prostate cancer mortality when compared with immediate prostatectomy
				D'Amico risk score High N = 103	HR: 0.38 (0.08, 1.89)	Prostate cancer deaths per 1000	111.1	43.8 (9.4, 199.6)	67 fewer (102 fewer, 89 more)	Very low[2]	For men with a high D'Amico risk score we are uncertain as to whether active surveillance results in a clinically **important (large)^** decrease in

											prostate cancer mortality when compared with immediate prostatectomy

CI = confidence interval; HR = hazard ratio; MCID = minimally important difference; N = number; NA = not available; PSA = prostate specific antigen; RCT = randomised controlled trial
[1] Downgraded by three levels due to serious concerns re risk of bias and indirectness, and very serious concerns re imprecision
[2] Downgraded by three levels due to serious concerns re risk of bias and indirectness, and extremely serious concerns re imprecision
[3] Downgraded by three levels due to serious concerns re indirectness and very serious concerns re imprecision
^ Using thresholds of 15, 30 and 60 deaths /1000 for small (minimal clinically important difference), moderate and large effects

Table 34. *Summary of findings for active surveillance based only on PSA monitoring vs immediate external beam radiotherapy (PICO10b)*

Outcome (MCID)	***Time frame (years)***	***RCTs (N)***	***Participants (N)***	***Study results and measurements***	***Absolute effect estimates***				***Certainty of evidence (GRADE)***	***Plain text summary***
					Metric	***Immediate EBRT***	***Active surveillance (95% CI)***	***Difference (95% CI)***		
Prostate cancer-specific deaths (15/1000)	15 (median)	1	1090	HR: 1.14 (0.57, 2.27)	Prostate cancer deaths per 1000	29.3	33.3 (16.8, 65.3)	4 more (13 fewer, 36 more)	Very low[3]	We are uncertain as to whether active surveillance results in a clinically **unimportant^ i**ncrease in prostate cancer mortality when compared with immediate radiotherapy.
All-cause deaths (15/1000)	15 (median)	1	1090	HR: 1.14 (0.88, 1.47)	Death due to any cause per 1000	211.0	236.7 (188.2, 294.2)	26 more (23 fewer, 83 more)	Very low[2]	We are uncertain as to whether active surveillance results in a clinically **important (small)^** increase in mortality when compared with immediate radiotherapy.
Metastatic disease (30/1000)	15 (median)	1	1090	HR: 2.08 (1.30, 3.33)	Metastatic disease per 1000	49.5	100.2 (63.9, 155.5)	51 more (14 more, 106 more)	Low[1]	Active surveillance may result in a clinically **important (small)^^** increase in metastatic prostate cancer diagnoses when compared with immediate radiotherapy.
Sexual quality of life (11.6)*	2	1	740	Measured by: EPIC sexual summary score Scale: 0-100 Higher better	Mean EPIC sexual summary score	43.4 (mean)	48.2 (mean) (44.4, 52.0)	MD: 4.8 more (1.0 more, 8.6 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in sexual quality of life when compared with immediate radiotherapy
Sexual bother (14.8)*	2	1	744	Measured by: EPIC sexual bother score Scale: 0-100 Higher better	Mean EPIC sexual bother score	57.9 (mean)	61.2 (mean) (57.2, 67.2)	MD: 4.3 more (0.7 less, 9.3 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in sexual bother when compared with immediate radiotherapy
Bowel quality of life (4.1)*	2	1	785	Measured by: EPIC bowel summary score	Mean EPIC bowel summary score	89.3 (mean)	93.2 (mean) (91.6, 94.8)	MD: 3.9 more (2.3 more, 5.5 more)	Very low[4]	We are uncertain as to whether active surveillance results in a clinically **unimportant*^** increase in

				Scale: 0-100 Higher better						bowel quality of life when compared with immediate radiotherapy
Bowel bother (4.9)*	2	1	789	Measured by: EPIC bowel bother score Scale: 0-100 Higher better	Mean EPIC bowel bother sub-scale score	89.2 (mean)	94.2 (mean) (92.2, 96.2)	MD: 5.0 more (3.0 more, 7.0 more)	Very low[4]	We are uncertain as to whether active surveillance results in a clinically **important** (**small) *^** decrease in bowel bother when compared with immediate radiotherapy
Urinary quality of life (4.5)*	2	1	785	Measured by: EPIC urinary summary score Scale: 0-100 Higher better	Mean EPIC urinary summary score	91.4 (mean)	90.3 (mean) (88.8, 91.8)	MD: 1.1 less (2.6 less, 0.4 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in urinary quality of life when compared with immediate radiotherapy
Urinary bother (5.8)*	2	1	781	Measured by: EPIC urinary bother score Scale: 0-100 Higher better	Mean EPIC urinary bother sub-score	90.3 (mean)	88.6 (mean) (86.8, 90.4)	MD: 1.7 less (3.5 less, 0.1 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in urinary bother when compared with immediate radiotherapy
Anxiety (1.7)*	2	1	937	Measured by: HADS anxiety sub score Scale: 0-21 Lower better	Mean HADS anxiety sub score	3.7 (mean)	3.9 (mean) (3.5, 4.3)	MD: 0.2 more (0.2 less, 0.6 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in anxiety when compared with immediate radiotherapy.

CI = confidence interval; EBRT = external beam radiation therapy; HADS - = hospital anxiety and depression scale; HR = hazard ratio; MCID = minimally important difference; MD = mean difference; N = number; PSA = prostate specific antigen; RCT = randomised controlled trial

** Half the standard deviation of the **baseline** scores for the study for which results reported (Protect Trial)*

*** Half the standard deviation of the **baseline** scores estimated using GraphReader from Figure 4a in Weigel 2021, the study for which results reported*

[1] Downgraded by two levels due to serious concerns re imprecision and indirectness

[2] Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness

[3] Downgraded by three levels due to very serious concerns re imprecision and serious concerns re indirectness

[4] Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision

[5] Downgraded by two levels due to serious concerns re risk of bias and indirectness

^ Using thresholds of 15, 30 and 60 deaths /1000 for small (minimal clinically important difference), moderate and large effects

^^ Using thresholds of 30, 60 and 120 metastatic disease diagnoses /1000 for small (minimal clinically important difference), moderate and large effects

**^ Using thresholds of MCID (half standard deviation of baseline score), 2 x MCID and 4 x MCID for small (minimal clinically important difference), moderate and large effects*

Table 35. *Summary of findings for active surveillance based only on PSA monitoring vs immediate external beam radiotherapy by age and D'Amico risk score subgroups*

Outcome (MCID)	*Time frame (years)*	*RCTs (N)*	*Participants (N)*	*Subgroup*	*Study results*	*Absolute effect estimates*				*Certainty of evidence (GRADE)*	*Plain text summary*
						Metric	*Immediate EBRT*	*Active surveillance (95% CI)*	*Difference (95% CI)*		
Prostate cancer-specific deaths (15/1000)	15 (median)	1	1090	Age < 65 years N = 681	HR: 0.49 (0.17, 1.43)	Prostate cancer deaths per 1000	29.3	14.5 (5.0, 41.6)	15 fewer (24 fewer, 12 more)	Very low[3]	For men aged < 65 years we are uncertain as to whether active surveillance results in a clinically **important (small)^** decrease in prostate cancer mortality when compared with immediate radiotherapy.
				Age ≥ 65 years N = 409	HR: 2.33 (0.87, 6.25)	Prostate cancer deaths per 1000	29.4	67.2 (25.6, 170.1)	38 more (4 fewer, 141 more)	Very low[3]	For men aged ≥ 65 years we are uncertain as to whether active surveillance results in a clinically **important (moderate)^** increase in prostate cancer mortality when compared with immediate radiotherapy.
	15 (median)	1	1015	D'Amico risk score Low N = 671	HR: 1.59 (0.56, 4.35)	Prostate cancer deaths per 1000	17.5	27.7 (9.8, 73.9)	10 more (8 fewer, 56 more)	Very low[1]	For men with a low D'Amico risk score we are uncertain as to whether active surveillance results in a clinically **unimportant^** increase in prostate cancer mortality when compared with immediate radiotherapy
				D'Amico risk score Intermediate N = 251	HR: 0.61 (0.15, 2.56)	Prostate cancer deaths per 1000	41.0	25.2 (6.3, 101.6)	16 fewer (35 fewer, 61 more)	Very low[2]	For men with an intermediate D'Amico risk score we are uncertain as to whether active surveillance results in a clinically **important (small)^** decrease in prostate cancer mortality when compared with immediate radiotherapy
				D'Amico risk score High N = 93	NA	Prostate cancer deaths per 1000	0	NA			No evidence available for men with a high D'Amico risk score

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; MCID = minimally important difference; N = number; NA = not available; PSA = prostate specific antigen; RCT = randomised controlled trial

[1] Downgraded by three levels due to serious concerns re risk of bias and indirectness, and very serious concerns re imprecision

[2] *Downgraded by three levels due to serious concerns re risk of bias and indirectness, and extremely serious concerns re imprecision*
[3] *Downgraded by three levels due to serious concerns re indirectness and very serious concerns re imprecision*
^ *Using thresholds of 15, 30 and 60 deaths /1000 for small (minimal clinically important difference), moderate and large effects*

5. Ongoing clinical trials

One potentially relevant trial protocol was identified by searches of clinical trial registries and literature searches. This trial was terminated as it was not meeting accrual target. No potentially relevant ongoing trials were identified other than those included in this systematic review.

Table 36. *Summary of potentially relevant ongoing or terminated randomised controlled trials comparing active surveillance with radical prostatectomy or radiotherapy.*

Study ID	*Study name and location*	*Start date*	*Completion date*	*Status*	*Population*	*Intervention*	*Comparator*	*Outcomes*
NCT00499174 ACTRN12611000027910	Observation or radical treatment in patients with prostate cancer - A phase III study of active surveillance therapy against radical treatment in patients diagnosed with favourable risk prostate cancer (START) Australia, Canada, New Zealand and USA	June 2007	October 2013	Terminated (not meeting accrual target)	Males aged 18 years and older, with histologically confirmed prostate adenocarcinoma classified as favourable risk (localised, Gleason score ≤ 6 and PSA ≤ 10 ng/ml) diagnosed within 6 months of randomisation. No previous treatment for prostate cancer including surgery, radiotherapy or androgen deprivation therapy for greater than 3 months.	Active surveillance	Radical prostatectomy or radiotherapy based on patient and physician preference within 90 days of randomisation	Disease-specific survival Overall survival Distant disease-free survival Quality of life anxiety

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APPENDICES

Appendix A:

A.1 Search strategies used for the 2016 guidelines

Database: Medline

#	*Search terms*
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	randomized controlled trial.pt.
5	controlled clinical trial.pt.
6	placebo.ab.
7	randomi?ed.ab.
8	randomly.ab.
9	trial.ab.
10	groups.ab.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp animals/ not humans.sh.
13	11 not 12
14	(active adj2 surveillance).mp
15	(expectant$ adj2 (management or treat$)).mp
16	delay$ intervention.mp
17	(active adj1 monitoring).tw
18	'active monitoring'.tw
19	'conservative monitoring'.tw
20	'delayed treatment$'.tw
21	'watchful observation'.tw
22	'watchful surveillance'.tw
23	'watchful monitoring'.tw
24	'expectant monitoring'.tw
25	'expectant surveillance'.tw
26	'delayed therap$'.tw
27	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	3 AND 13 AND 27

Used the Cochrane sensitivity maximizing filters for identifying randomised controlled trials (http://handbook.cochrane.org, accessed 20/02/2013/ Centre for Reviews and Dissemination systematic review/ meta-analyses strategy 2 (Lee et al, (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology 12:51)

Search terms used to identify Aboriginal and Torres Strait Islander populations

#	*Search terms*
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	prostate cancer.mp. or exp Prostatic Neoplasms/
4	1 AND (2 OR 3)

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

Database: Embase

#	*Search terms*
1	'prostate cancer'/exp OR 'prostate cancer'
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
3	#1 OR #2
4	active NEAR/2 surveillance
5	expectant* NEAR/2 (management OR treat*)
6	delay* NEAR/3 intervention
7	#4 OR #5 OR #6
8	rct
9	'randomized controlled trial'/exp OR 'randomized controlled trial'
10	'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'randomized controlled trials'/exp OR 'randomized controlled trials' OR 'randomised controlled trials'
11	'random allocation'/exp OR 'random allocation'
12	'randomly allocated'
13	'randomization'/exp OR 'randomization'
14	allocated NEAR/2 random
15	'double blind procedure'/exp OR 'double blind procedure'
16	'single blind procedure'/exp OR 'single blind procedure'
17	single NEXT/1 blind*
18	double NEXT/1 blind*
19	(treble OR triple) NEXT/1 blind*
20	placebo*
21	'placebo'/exp OR 'placebo'
22	'prospective study'/exp OR 'prospective study'
23	'crossover procedure'/exp OR 'crossover procedure'
24	'clinical trial'/exp OR 'clinical trial'
25	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26	#3 AND #7 AND #25

Search terms used to identify Aboriginal and Torres Strait Islander populations

#	*Search terms*
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

Databases: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews and Health Technology Assessment database

#	*Search terms*
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 OR 2

A.2 Search strategy used for the 2025 guidelines update

Databases: Medline, Embase and CENTRAL databases (via Ovid platform)

#	*Search terms*
1	exp Prostatic Neoplasms/
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta*)).tw.
3	1 or 2
4	Watchful Waiting/
5	((active* or watch* or expect* or conservat*) adj2 (surveillan* or monitor* or observat* or wait* or manag*)).tw.
6	((deferr* or delay*) adj2 (treat* or therap*)).tw.
7	4 or 5 or 6
8	3 and 7
9	Prostatic Neoplasms/su
10	exp Prostatectomy/
11	prostatectom*.tw.
12	(radical adj1 (therap* or treat*)).tw.
13	9 or 10 or 11 or 12
14	exp Radiotherapy/
15	radiotherap*.tw.
16	((radiat* or radio*) adj4 (therap* or treat*)).tw.
17	((interstitial* or intracavit* or implant* or surface* or internal* or external* or conform* or seed*) adj4 (irradiat* or radiation* or radio* or therap* or treat*)).tw.
18	(brachytherap* or curietherap*).tw.
19	EBRT.tw.
20	((seed* or permanent*) adj2 implant*).tw.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	13 or 21
23	8 and 22
24	randomized controlled trial.pt.
25	controlled clinical trial.pt.
26	randomi?ed.tw.
27	randomly.tw.
28	trial.tw.
29	RCT*.tw.
30	groups.tw.
31	24 or 25 or 26 or 27 or 28 or 29 or 30
32	23 and 31
33	conference abstract.pt.
34	32 not 33
35	limit 34 to english language
36	limit 35 to yr="2018 -Current"
37	remove duplicates from 36

Used a modified Cochrane sensitivity maximizing filter for identifying randomized controlled trials in Medline (https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies; accessed 28/08/2023).

Appendix B: GRADE assessment of the certainty of the evidence

Grade	*Definition*
⊕⊕⊕⊕ High certainty	We are very confident that the true effect lies close to that of the estimate of the effect.
⊕⊕⊕◯ Moderate certainty	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ Low certainty	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
⊕◯◯◯ Very low certainty	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix C: Excluded studies - 2016 guidelines systematic review

Study	*Reason for Exclusion*
Bastian 2009	Review with inappropriate study design
Bul 2012	Inappropriate study design. Not randomised.
Dahabreh 2012	Inappropriate study design. No appropriate data in paper.
Godtman 2013	Inappropriate study design. Single-arm AS cohort study.
Heidenreich 2011	EAU guidelines. No appropriate data in paper.
Khatami 2006	Inappropriate study design. Not biopsy determined PCa.
Khatami 2009	Biomarker analysis. No appropriate data in paper.
Klotz 2004	Inappropriate study design. No appropriate data in paper.
Klotz 2008	No appropriate data in paper.
Klotz 2010	Inappropriate study design. No appropriate data in paper.
Lane 2010	No appropriate data in paper.
Mhaskar 2012	No appropriate data in paper.
Mullins 2013	Inappropriate study design. No appropriate data in paper.
Roach 2012	Inappropriate study design. Intervention is WW, not AS.
Roemeling 2006	Inappropriate study design. Intervention (WW not AS) not randomised.
Roemeling 2007a (EU)	Inappropriate study design. Intervention not randomised.
Roemeling 2007b (C)	Inappropriate study design
van den Bergh 2010	Inappropriate study design
Wever 2013	Inappropriate study design
Wilt 1994	Inappropriate study design. A RCT with WW as the intervention
Wilt 1995	Inappropriate study design. A RCT with WW as the intervention.
Wilt 1997	No appropriate data in paper.
Wong 2012	Inappropriate study design. No appropriate data in paper.

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Wilt TJ, Brawer MK. The Prostate cancer Intervention versus Observation Trial (PIVOT): A randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *Cancer* 1995; 75:1963-8.

Wilt TJ, Brawer MK. The Prostate Cancer Intervention versus Observation Trial (PIVOT). *Oncology* 1997; 11(8):1133-43.

Wong LM, Neal DE, Johnston RB, Shah N, Sharma N, Warren AY et al. International multicentre study examining selection criteria for active surveillance in men undergoing radical prostatectomy. *British Journal of Cancer* 2012; 107:1467-73.

Appendix D: Excluded studies - 2025 review update

Article	*PMID/DOI*	*Reason for exclusion*
Achard 2021	https://dx.doi.org/10.1159/000513258	Excluded publication type
Ahlberg 2019	https://dx.doi.org/10.1136/bmjopen-2018-027860	Excluded publication type
Albers 2021	https://doi.org/10.1007/s00345-020-03154-7	No comparative data
Bill-Axelson 2018	https://dx.doi.org/10.1056/NEJMoa1807801	No comparator of interest
Bryant 2020	https://dx.doi.org/10.1111/bju.14987	No outcome of interest
Carlsson 2019	https://dx.doi.org/10.1016/j.eururo.2019.03.010	No comparator of interest
Chan 2021	https://dx.doi.org/10.3390/cancers13133274	Systematic review with different inclusion criteria
Dahm 2020	PMID: 32986341	No comparator of interest
Degeling 2021	https://dx.doi.org/10.1016/j.jval.2021.06.004	Excluded publication type
Donovan 2019	https://dx.doi.org/10.1016/j.jclinepi.2019.05.036	Excluded study design
Fenton 2018	https://dx.doi.org/10.1001/jama.2018.3712	Systematic review with different inclusion criteria
Godtman 2018	https://dx.doi.org/10.1016/j.juro.2018.04.078	No population of interest
Hamdy 2020	https://dx.doi.org/10.3310/hta24370	Excluded publication type
Lane 2022	https://dx.doi.org/10.1111/bju.15739	Superseded by more recent publication
Luo 2021	https://dx.doi.org/10.1177/1457496919883962	Systematic review with different inclusion criteria
Neal 2020	https://dx.doi.org/10.1016/j.eururo.2019.10.030	Superseded by more recent publication
Ng 2019	https://dx.doi.org/10.1177/2051415818812316	Systematic review with different inclusion criteria
Nouhi 2019	https://dx.doi.org/10.18502/ijph.v8i4.978	Systematic review with different inclusion criteria
Johansson 2018	https://dx.doi.org/10.1016/j.euo.2018.03.003	No comparator of interest
Thomsen 2019	https://dx.doi.org/10.1016/j.clgc.2019.05.005	Excluded study design
Tiruye 2022	https://dx.doi.org/10.1186/s12894-022-01117-1	Excluded study design
Vernooij 2021	https://doi.org/10.1002/14651858.CD006590.pub3	Systematic review with overlapping inclusion criteria. Included ProtecT trial studies (Hamdy 2016, Donovan 2016) included in this systematic review and superseded by more recent studies.
Wade 2020	https://dx.doi.org/10.1136/bmjopen-2019-036024	No outcome of interest
Wilt 2020	https://dx.doi.org/10.1016/j.eururo.2020.02.009	No comparator of interest

Appendix E: International Society Urological Pathology Gleason Grade Groups:

Group 1 have a Gleason score of ≤ 6 (3+3), associated with low risk of progression;

Group 2 have Gleason score of 7 (3+4), associated with favourable intermediate risk of progression;

Group 3 have a Gleason score of 7 (4+3), associated with intermediate risk of progression;

Groups 4 and 5 have Gleason scores of ≥ 8, associated with high risk of progression.

3.17 Clinical question 11 – Active Surveillance PICO 11A and 11B

Clinical question 11: *What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?"*

Introduction

For the 2016 guidelines a systematic review was undertaken of randomised controlled trials and non-randomised studies comparing active surveillance with immediate treatment for localised prostate cancer to identify active surveillance protocols with long term outcomes comparable to those for immediate treatment. Three cohort studies were included; no randomised controlled trials were found. The 2016 guidelines did not consider comparisons of different active surveillance protocols. Following the publication of the 2016 guidelines the results of the ProtecT trial were published; a randomised controlled trial comparing active surveillance with immediate treatment. Consequently, to address this clinical question for this guideline update:

- The selection criteria for the update of the systematic review of comparisons of active surveillance with immediate treatment for localised prostate cancer were revised to include randomised controlled trials only, and
- A second systematic review was undertaken to identify randomised controlled trials comparing different active surveillance protocols.

This is the report for the first systematic review.

Systematic review report – Randomised controlled trials comparing of active surveillance with immediate definitive treatment for people diagnosed with localised prostate cancer

Authors

Denise Campbell, Isabel Rewais, Chelsea Carle, Rehana Abdus Salam, Susan Yuill, Michael David, Sam Egger, Suzanne Hughes

PICOs

This systematic review addresses the following PICOs which are summarised in detail in Tables 1a and 1b.

PICO 11a. *For individuals with biopsy-diagnosed localised prostate cancer, which active surveillance protocols achieve equivalent or better outcomes in terms of length and quality of life than immediate prostatectomy?*

PICO 11b. *For individuals with biopsy-diagnosed localised prostate cancer, which active surveillance protocols achieve equivalent or better outcomes in terms of length and quality of life than immediate radiotherapy?*

Table 34a. *PICO 11a components*

Population	*Intervention*	*Comparator*	*Outcomes*	*Study design*
Individuals with biopsy-confirmed localised prostate cancer (cT1-2)	Active surveillance	Immediate prostatectomy	All-cause mortality Prostate cancer-specific mortality Metastasis Health-related quality of life Adverse patient-reported outcomes	Randomised controlled trials or systematic reviews thereof

Table 1b. *PICO 11b components*

Population	*Intervention*	*Comparator*	*Outcomes*	*Study design*
Individuals with biopsy-confirmed localised prostate cancer (cT1-2)	Active surveillance	Immediate radiotherapy	All-cause mortality Prostate cancer-specific mortality Metastasis Health-related quality of life Adverse patient-reported outcomes	Randomised controlled trials or systematic reviews thereof

1. Methods

1.1 Revised selection Criteria

Table 2. *Selection criteria for systematic review of randomised controlled trials comparing active surveillance to immediate definitive treatment for individuals diagnosed with localised prostate cancer.*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	Nomograms (or predictive model) studies
Study design	Randomised controlled trials or systematic reviews thereof	
Population	Individuals with biopsy-confirmed and localised (cT1-2) prostate cancer Or Subgroups thereof	Studies that restricted participants based on biomarker status More than 10% > cT2 prostate cancer and no subgroup analyses
Intervention	Active surveillance – monitored for disease progression and offered definitive/curative therapy, i.e., prostatectomy or radiotherapy (external beam radiation therapy or brachytherapy) if progression evident	Watchful waiting (men not necessarily offered definitive/curative therapy if disease progresses rather offered treatments to manage symptoms)
Comparator	Immediate definitive/curative treatment: Radical prostatectomy, or External beam radiation therapy, or Brachytherapy	ADT alone Systemic treatment only
Outcome	All-cause mortality Prostate cancer-specific mortality Metastasis (nodal and/or distant) Overall health-related quality of life Adverse patient-reported outcomes: Urinary function/bother Sexual function/bother Bowel function/bother Anxiety Depression	Disease progression
Publication date	1st January 1990 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

ADT = androgen deprivation therapy

1.2 Definitions and terminology

For the purposes of this review:

Localised prostate cancer refers to cancer that is confined within the prostate, classified as clinical stage <T3 (Bruinsma 2017)

Active surveillance is a monitoring strategy for men with localised prostate cancer. It aims to minimise treatment-related toxicity without compromising survival by achieving correct timing for curative treatment for those who may eventually require it.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website
- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website

- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- Urological Society of Australia and New Zealand (USANZ) website
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e., be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and be published from 2023 onwards so as to include recent published results. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence i.e., did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

This systematic review covers the literature published from January 1990 onwards.

For the 2016 guidelines systematic review, Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched from 1990 using text terms and, where available, database-specific subject headings. Each database was searched for articles dealing with prostate cancer. In Medline and Embase databases the prostate cancer search was coupled with a search for active surveillance and a filter for randomised controlled trials. To identify studies which considered Aboriginal and Torres Strait Islander peoples these searches were then coupled with search terms for Aboriginal and Torres Strait Islander peoples. A complete list of the terms used for all search strategies are included as Appendix A. Monthly alerts were established for both Medline and Embase searches to identify relevant articles published before 1st March 2014 which were either published after the initial search was completed and/or added to the relevant database after the search was completed. Alerts were checked until July 2014. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment databases were searched regularly up until April 2014 for relevant reviews published after the initial search. Reference lists of all relevant articles were checked for potential additional articles.

For the 2025 update of this systematic review, assessment of existing guidelines identified a systematic review for the NICE guideline NG131: Prostate cancer: diagnosis and management (NICE 2019) that adequately captured the relevant literature published from January 1990 to March 2018. We assessed the

studies included in this review for inclusion in our systematic review and undertook literature searches to identify randomised controlled trials or systematic reviews thereof published from 2018 onwards. Medline, Embase and Cochrane CENTRAL databases were searched on 28th August 2023 combining text terms and database-specific subject headings for prostate cancer, active surveillance, radical prostatectomy, radiation therapy and a filter for randomised controlled trials. Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st September 2024. A complete list of the terms used in the search is included as Appendix A. In addition, the Cochrane Database of Systematic Reviews was searched on 13th March 2024 using the search term "prostate". The searches were designed to identify potentially relevant trials in populations that included Aboriginal and Torres Strait Islander peoples. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

Two reviewers independently extracted data from the included studies (with independent third-reviewer adjudication if needed). The following data was extracted from included studies: Country and year of publication, participant eligibility and age, duration of follow-up, intervention details including the active surveillance monitoring protocol and triggers for change to treatment, comparator details including description of the definitive treatment and any concurrent treatments, participant characteristics for intervention and comparator groups including age, PSA level, Gleason score, ISUP Grade Group and clinical stage, and relevant outcomes reported, and additional information including notable study limitations.

The hazard ratio or crude risk ratio and 95% confidence interval for the intention-to-treat analyses were extracted as reported in the study or were calculated using relevant data. Where a study reported definitive treatment as the intervention and active surveillance as the comparator, published hazard ratios and 95% confidence intervals were inverted to reframe active surveillance as the intervention. Crude risk ratios were calculated as the absolute risk (number of events divided by number of participants) per 1000 in the intervention group divided by the absolute risk per 1000 in the comparator group. For patient-reported outcome measures reporting mean scores, mean and standard deviation values were extracted allowing for calculation of the mean difference and 95% confidence interval using an online statistical calculator (MedCalc Software Ltd. 2024). Pooled analyses were planned where there were two or more studies reporting the same outcome at corresponding time points. For the summary of finding tables where the effect estimate was a hazard ratio the estimated risk of the outcome in ethe intervention arm and its 95% confidence interval were calculated using the following formula:

$$1000 \times (1 - S(t)^{HR})$$

where *S(t)* is the estimated probability of no event in the control arm and *HR* is the hazard ratio for the event (Case 2002).

1.6 Risk of bias assessments

Two reviewers independently assessed the risk of bias of outcomes in each included study (with independent third-reviewer adjudication as needed) using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) (Sterne 2019). The overall risk of bias for each outcome for each outcome was rated low, some concerns

or high for the following sources of bias; the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for each outcome determined to be critical by the Active Surveillance Working Group (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Schunemann 2013) and Schunemann et al 2022, and on guidance for assessing narrative syntheses provided by Murad 2017. For the assessment of risk of bias missing outcome data and measurement of the outcome related to lack of clinician and patient blinding to the group assignment and self-report of the outcome for patient-reported outcomes were considered important potential sources of bias.

Imprecision was assessed using thresholds for a minimal clinically important difference (MCID) and for moderate and large absolute effects. For dichotomous outcomes, these thresholds were determined by a reference group consisting of a consumer, a general practitioner, a urology nurse practitioner and clinical specialists following GRADE guidance provided by Schunemann 2022. For continuous patient reported outcomes, based on methods published for individuals diagnosed with localised prostate cancer (Skolarus 2015, Umbehr 2018, Mazariego 2020) and advice from experts, MCIDs were calculated as the half the standard deviation for that outcome of the population at baseline. Where baseline standard deviations were reported only for each arm of a trial, the baseline standard deviation for the entire population was calculated using the formula:

$$s_p = \sqrt{\frac{(n_1 - 1)\, s_1^2 + (n_2 - 1)\, s_2^2}{n_1 + n_2 - 2}}$$

where n_1 = number of participants in arm 1, n_2 = number of participants in arm 2, s_1 = standard deviation for arm 1 and s_2 = standard deviation for arm 2 (Fisher 1970). Imprecision was assessed in the context of whether there was a clinically important increase or decrease. Potential publication bias (or small study effects) was assessed using a Funnel Plot if 10 or more studies. Where there were less than 10 studies clinical trial registries were searched for potentially relevant trials (see Section 1.8 below for search details) that planned to report long term outcomes and commenced before 2007 (with over 15 years of follow-up), and trials that planned to report patient-reported outcomes and commenced before 2017 (with over 5 years of follow-up), that had not been terminated and for which results had not been published, suggesting publication bias.

The Active Surveillance Working Group determined critical outcomes prior to the assessment of the evidence. Patient-reported outcomes were considered critical at two years; a timepoint where the outcomes would be impacted by the long-term rather than the short-term effects of immediate treatment, before being affected by aging and the substantial uptake of active treatments amongst those randomised to active surveillance.

As per GRADE guidance, randomised controlled trials started with a high level of certainty in the evidence and were downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

Definitions of the GRADE ratings of certainty of the overall body of evidence are presented in Appendix B.

1.8 Clinical trial registry searches

Potentially relevant ongoing or unpublished trials were identified from literature and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing and unpublished randomised controlled trials registered or posted by 16th September 2024 using the search terms listed below:

Clinicaltrials.gov using the terms:

"prostate cancer" and "surveillance"

"prostate cancer" and "active surveillance"

International Clinical Trials Registry Platform (https://trialsearch.who.int/Default.aspx) using the terms:

"active surveillance" and "prostate cancer"

"radical prostatectomy" and "prostate cancer"

"comparative effectiveness" and "surgery" and "prostate cancer"

"comparative effectiveness" and "radiation therapy" and "prostate cancer"

"radiotherapy" and "prostate cancer"

"prostate cancer" and "active monitoring"

"prostate cancer" and "delayed treatment"

2. Results

2.1 Guidelines searches

No relevant guidelines published from 2023 onwards were identified which were reportedly based on systematic reviews of the literature.

2.2 Literature searches

Figure 1 outlines the process of inclusion and exclusion of articles from the 2016 guidelines systematic review and 2025 updated systematic review. For this update, the search of the Cochrane Database of Systematic Reviews did not identify any potentially relevant systematic reviews. The combined search of Medline and Embase retrieved 485 records after removal of duplicates. Titles and abstracts were examined by two reviewers and 26 articles were retrieved for a more detailed evaluation. An additional three potentially relevant articles were identified from the NICE guidelines systematic review (NICE 2019) and reference lists for more detailed evaluation. Two reviewers independently assessed the full texts. The update identified five articles reporting on two randomised controlled trials that met the revised selection criteria for inclusion; four articles reported on the ProtecT trial and one reported on the PREFERE trial. No articles from the 2016 guidelines systematic review met the revised selection criteria. There were no studies that included of Aboriginal and/or Torres Strait Islander peoples that met the selection criteria. The retrieved articles that were not included in the previous review and this review update along with the reasons for their exclusion are documented in Appendices C and D. For the review update the main reasons for exclusion were no comparator of interest and systematic review with different inclusion criteria.

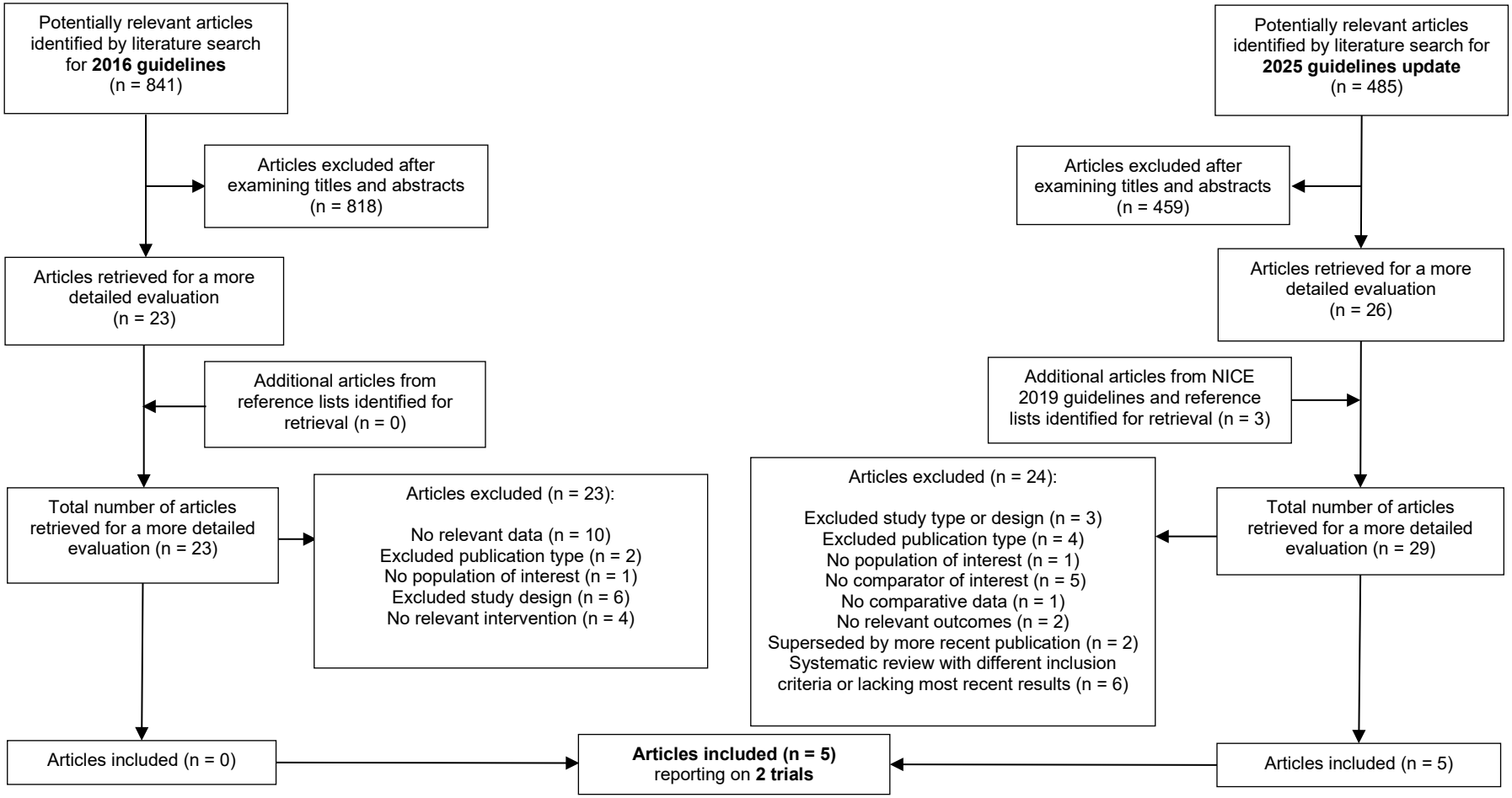

Figure 1. *Process of inclusion and exclusion of published articles from the 2016 guidelines systematic review and 2025 systematic review update*

2.3 Characteristics of included studies

The characteristics of studies included in the systematic review are described in Table 3.

Table 3. *Study characteristics of included randomised controlled trials comparing active surveillances to immediate definitive treatment for men diagnosed with localised prostate cancer.*

Study	*Participants*	*Intervention*	*Comparator: Immediate definitive treatment*	*Outcomes of interest*	*Comments*
ProtecT Trial RCT United Kingdom **Hamdy 2023 & 2016, Donovan 2023 & 2016**	Men aged 50-69 years with a life expectancy ≥10 years contacted via 337 primary care centres in 9 cities and invited to undergo a PSA test in 1999-2009. Eligible men* with a PSA level 3-19.9 ng/ml and histopathological diagnosis of clinically localised prostate cancer (cT1c-T2, NX, M0) on 10-core biopsy were enrolled. Median follow-up: 15 years **N = 1643**	**Active Monitoring –** No confirmatory biopsy <u>Monitoring protocol:</u> PSA monitoring (test every 3 months in year 1, then every 3-6 months). Annual specialist nurse review. Urologist review including DRE if • requested by clinician or patient • disease progression suspected based on: ○ symptomatic disease (urinary or systematic) ○ >20% PSA increase on consecutive measurements, sustained at 3 months ○ ≥50% PSA increase in 12-month period confirmed by repeat tests. <u>Triggers for offering treatment:</u> Disease progression based on restaging and review of PSA patterns, clinical stage and disease grade. Treatment options discussed based on disease grade and clinical stage. Treatment determined by joint clinician-patient decision making. **N = 545** Median age (range): 62 (50-69) years Median PSA (range): 4.6 (3.0-20.9) ng/ml Gleason score ≤6: 77%, 7: 20%	**Radical Prostatectomy** + lymphadenectomy if GS≥7 or PSA ≥10 ng/ml ± adjuvant or salvage radiotherapy (discussed with urologist if positive surgical margins, extracapsular disease, or post-operative PSA level ≥0.2 ng/ml) PSA monitoring (test every 6 months in year 1, then every 6-12 months). **N = 553** Median age (range): 62 (50-69) years Median PSA (range): 4.7 (3.0-18.4) ng/ml Gleason score ≤6: 76%, 7: 22% ISUP Grade Group 1: 77%, 2: 18%, ≥3: 5% Clinical stage T1c: 74%, T2: 26% **External Beam Radiation Therapy** + neoadjuvant and concomitant ADT PSA monitoring (test every 6 months in year 1, then every 12 months). Oncologist review if PSA levels rise by ≥2.0 ng/ml post-nadir or if concerns raised about clinical progression. **N = 545** Median age (range): 62 (49-69) years Median PSA (range): 4.6 (3.0-18.8) ng/ml Gleason score ≤6: 78%, 7: 20% ISUP Grade Group 1: 78%, 2: 15%, ≥3: 7% Clinical stage T1c: 79%, T2: 21%	**Primary outcome:** Prostate cancer-specific mortality **Secondary outcomes:** All-cause mortality Metastatic disease **Patient-reported outcomes:** Urinary function and QoL Sexual function and QoL Bowel function and QoL Overall health-related QoL Anxiety Depression	Study designed to determine the most clinically- and cost-effective method of treating men with clinically localised prostate cancer. In all arms, ADT offered to men if PSA level ≥20 ng/ml, or less if indicated, and skeletal imaging recommended if PSA level ≥10 ng/ml. Details of what constituted disease progression as a trigger for offering definitive treatment were not reported in any of the included articles 488 men underwent RP within 12 months of randomisation (irrespective of allocation): 138/484 (29%) cT1-T2 upstaged to pT3-T4 on RP; 155/483 (32%) ISUP Grade Group** upgraded on RP; 133/363 (37%) upgraded from ISUP Grade Group 1 to ≥2 on RP. Metastatic disease included regional node disease

Study	*Participants*	*Intervention*	*Comparator: Immediate definitive treatment*	*Outcomes of interest*	*Comments*
		ISUP Grade Group** 1: 77%, 2: 17%, ≥3: 6% Clinical stage T1c: 75%, T2: 25%			
PREFERE trial RCT **(non-inferiority)** Germany **Wiegel 2021**	Men aged 18-75 years with a life expectancy ≥10 years recruited via 69 study centres from 2012-2016. Eligible men^ with ECOG performance status 0-1, IPSS score <18, PSA a level ≤10 ng/ml and histopathological diagnosis of localised prostate cancer (≤cT2a, NX, M0) with Gleason score ≤7(3+4) were enrolled. **Trial terminated early due to poor patient accrual.** Median follow-up: 19.7 months **N = 345** Age in years: <65: 46%, 65-70: 26%, 71-75: 28% PSA ≤6 ng/ml: 52%, >6 ng/ml: 48% Gleason score ≤6: 65%, 7(3+4): 35%	**Active Surveillance** <u>Monitoring protocol:</u> Confirmatory biopsy at 6 months, re-biopsy after 12 months for GS 6 and after 3 and 12 months for GS 7, then re-biopsy every 3 years up to age 80. Recommended follow-up of PSA test and DRE every 3 months in years 1-2, then every 6 months. <u>Triggers for offering treatment:</u> AS terminated if requested by the patient, or if histological reclassification observed at re-biopsy (ISUP Grade Group** 1 to ≥2, or 2 to ≥3), tumour volume of ISUP Grade Group 2 tumours exceeded ≥ 33% of biopsy cores, or if reclassification to pT3 observed. **N = 130**	**Radical Prostatectomy** + lymphadenectomy if GS 7(3+4) PSA monitoring (schedule NR). **N = 69**	**Patient-reported outcomes (available):** Overall health-related QoL Sexual activity **Primary and secondary outcomes unavailable due to trial termination:** Prostate cancer-specific survival Overall survival Distant metastases	Study designed to assess noninferiority of AS, EBRT, or brachytherapy by PSI to RP for men with low or early intermediate-risk prostate cancer, therefore AS vs EBRT and AS vs PSI not compared. Participants could exclude up to 2 of 4 modalities for randomisation, resulting in 11 different strata within the RCT. All primary biopsies were submitted to reference pathology to obtain a second expert's opinion, prior to randomisation. 114/459 (25%) men who consented to participate were excluded (87/114 due to reference pathology discrepancies). 40 (12%) patients changed from assigned treatment following randomisation.

AS = active surveillance; ADT = androgen deprivation therapy; BPH = benign prostatic hyperplasia; DRE = digital rectal examination; EBRT = external-beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; GS = Gleason Score; IPSS = International Prostate Symptom Score; ISUP = International Society for Urological Pathology; n/a = not available; NR = not reported; PSA = prostate-specific antigen; PSI = permanent seed implantation; QoL = quality of life; RCT = randomised controlled trial; RP = radical prostatectomy
** ProtecT trial exclusion criteria: Men with previous malignancies (except skin cancer), renal transplant or on renal dialysis, major cardiovascular or respiratory comorbidities, bilateral hip replacement or estimated life expectancy of < 10 years were ineligible.*
^ PREFERE trial exclusion criteria: Men with prior treatment for malignancies (except skin cancer and low-risk urothelial cancer), prior surgery for BPH, American Society of Anaesthesiologists (ASA) score 4, proctitis, or use of alpha-blockers or 5-alpha-reductase inhibitors were ineligible. Men with the following contraindications to radiotherapy could be randomised to AS or RP: IPSS >18, residual urine >50 ml, prostate volume >60 ml, predominant middle lobe BPH, inflammatory bowel disease.
*** ISUP Grade Group definitions in Appendix E*

2.4 Results by outcomes of interest

Prostate cancer-specific mortality (median 10 and 15-year follow-up) – results are shown in Section 2.4.1, Table 4

All-cause mortality (median 10 and 15-year follow-up) – results are shown in Section 2.4.2, Table 5

Metastatic disease (median 10 and 15-year follow-up) – results are shown in Section 2.4.3, Table 6

Patient-reported outcomes:

Sexual (Section 2.4.4)

- Overall function and quality of life (1, 2, 6, and 12-year follow-up) – results are shown in Table 7
- Bother (1, 2, 6, and 12-year follow-up) – results are shown in Table 8
- Function (1, 2, 6, and 12-year follow-up) – results are shown in Table 9
- Activity (1 and 2-year follow-up) – results are shown in Table 10

Bowel (Section 2.4.5)

- Overall function and quality of life (1, 2, 6, and 12-year follow-up) – results are shown in Table 11
- Bother (1, 2, 6, and 12-year follow-up) – results are shown in Table 12
- Function (1, 2, 6, and 12-year follow-up) – results are shown in Table 13

Urinary (Section 2.4.6)

- Overall function and quality of life (1, 2, 6, and 12-year follow-up) – results are shown in Table 14
- Bother (1, 2, 6, and 12-year follow-up) – results are shown in Table 15
- Function (1, 2, 6, and 12-year follow-up) – results are shown in Table 16

Overall cancer-related quality of life (1, 2, 5 and 10-year follow-up) – results are shown in Section 2.4.7, Table 17

Anxiety (1, 2, 6, and 12-year follow-up) – results are shown in Section 2.4.8, Table 18

Depression (1, 2, 6, and 12-year follow-up) – results are shown in Section 2.4.9, Table 19

2.4.1 Prostate cancer-specific mortality

Table 4. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***prostate cancer-specific mortality^***

Studies (N)	***Follow-up*** *(median)*	***Participants (N)***	***Prostate cancer deaths / person-years (N)***		***Prostate cancer-specific mortality rate*** *per 1000 person-years (95% CI)*		***Hazard ratio*** *(95% CI)*
			Active surveillance	***Definitive treatment***	***Active surveillance***	***Definitive treatment***	
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1098	17 / 7633	12 / 7766	2.2 (1.4, 3.6)	1.5 (0.9, 2.7)	1.52 (0.72, 3.22)*
1 (Hamdy 2016, ProtecT)	10-year	1098	8 / 5393	5 / 5422	1.5 (0.7, 3.0)	0.9 (0.4, 2.2)	Not performed**
Active surveillance *with PSA monitoring vs immediate* ***external beam radiation therapy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1090	17 / 7633	16 / 7628	2.2 (1.4, 3.6)	2.1 (1.3, 3.4)	1.14 (0.57, 2.27)*
1 (Hamdy 2016, ProtecT)	10-year	1090	8 / 5393	4 / 5339	1.5 (0.7, 3.0)	0.7 (0.3, 2.0)	Not performed**

CI = confidence interval; N = number; PSA = prostate-specific antigen
^ Definite or probable prostate cancer mortality, as adjudicated by an independent cause-of-death committee
** Hazard ratios adjusted for trial centre, patient's age at baseline, Gleason score, and PSA level at baseline (log-transformed).*
*** Adjusted analysis not performed due to low number of events.*

2.4.2 All-cause mortality

Table 5. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***all-cause mortality***

Studies (N)	***Follow-up*** *(median)*	***Participants (N)***	***All-cause mortality / person-years (N)***		***All-cause mortality rate*** *per 1000 person-years (95% CI)*		***Hazard ratio**** *(95% CI)*
			Active surveillance	***Definitive treatment***	***Active surveillance***	***Definitive treatment***	
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1098	124 / 7633	117 / 7766	16.2 (13.6, 19.3)	15.0 (12.5, 18.0)	1.12 (0.87, 1.45)
1 (Hamdy 2016, ProtecT)	10-year	1098	59 / 5393	55 / 5422	10.9 (8.5, 14.1)	10.1 (7.8, 13.2)	Not performed**
Active surveillance *with PSA monitoring vs immediate* ***external beam radiation therapy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1090	124 / 7633	115 / 7628	16.2 (13.6, 19.3)	15.0 (12.5, 18.0)	1.14 (0.88, 1.47)
1 (Hamdy 2016, ProtecT)	10-year	1090	59 / 5393	55 / 5339	10.9 (8.5, 14.1)	10.3 (7.9, 13.4)	Not performed**

CI = confidence interval; N = number; PSA = prostate-specific antigen
** Hazard ratios adjusted for trial centre, patient's age at baseline, Gleason score, and PSA level at baseline (log-transformed).*
*** Adjusted analysis not performed due to low number of events.*

2.4.3 Metastatic disease

Table 6. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***metastatic disease^***

Studies (N)	***Follow-up*** *(median)*	***Participants (N)***	***Metastatic disease / person-years (N)***		***Metastatic disease rate*** *per 1000 person-years (95% CI)*		***Hazard ratio**** *(95% CI)*
			Active surveillance	***Definitive treatment***	***Active surveillance***	***Definitive treatment***	
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1098	51 / 7324	26 / 7594	7.1 (5.4, 9.3)	3.5 (2.4, 5.1)	2.13 (1.32, 3.45)
1 (Hamdy 2016, ProtecT)	10-year	1098	33 / 5268	13 / 5377	6.3 (4.5, 8.8)	2.4 (1.4, 4.2)	Not performed**
Active surveillance *with PSA monitoring vs immediate* ***external beam radiation therapy*** *(hazard ratio <1 favours active surveillance)*							
1 (Hamdy 2023, ProtecT)	15-year	1090	51 / 7324	27 / 7467	7.1 (5.4, 9.3)	3.7 (2.5, 5.4)	2.08 (1.30, 3.33)
1 (Hamdy 2016, ProtecT)	10-year	1090	33 / 5268	16 / 5286	6.3 (4.5, 8.8)	3.0 (1.9, 4.9)	Not performed**

CI = confidence interval; N = number; PSA = prostate-specific antigen
^ Metastatic disease defined as bony, visceral, or lymph-node metastases confirmed on imaging, or PSA level ≥100 ng/ml.
** Hazard ratios adjusted for trial centre, patient's age at baseline, Gleason score, and PSA level at baseline (log-transformed).*
*** Adjusted analysis not performed due to low number of events.*

2.4.4 Sexual quality of life, bother, and function

Overall sexual function and quality of life

Table 7. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***sexual quality of life: EPIC sexual summary*** *score (range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC sexual summary score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	688	51.6 (27.4)	30.1 (23.2)	21.5 (17.7, 25.3)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	757	48.2 (27.5)	33.4 (23.4)	14.8 (11.2, 18.4)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	891	40.6 (26.7)	32.3 (23.2)	8.3 (5.0, 11.6)
1 (Donovan 2023, ProtecT)	12-year	Overall	495	33.2 (25.2)	30.0 (22.3)	3.2 (-1.0, 7.4)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	681	51.6 (27.4)	43.2 (27.6)	8.4 (4.3, 12.5)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	740	48.2 (27.5)	43.4 (25.2)	4.8 (1.0, 8.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	877	40.6 (26.7)	41.3 (24.9)	-0.7 (-4.1, 2.7)
1 (Donovan 2023, ProtecT)	12-year	Overall	500	33.2 (25.2)	35.2 (22.8)	-2.0 (-6.2, 2.2)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Sexual bother

Table 8. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***sexual bother: EPIC sexual bother sub-scale score*** *(range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC sexual bother sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	691	67.9 (34.2)	44.6 (34.1)	23.3 (18.2, 28.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	766	62.2 (35.4)	47.0 (33.2)	15.2 (10.3, 20.1)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	882	57.9 (36.6)	51.4 (35.5)	6.5 (1.7, 11.3)
1 (Donovan 2023, ProtecT)	12-year	Overall	494	55.3 (38.5)	54.3 (36.4)	1.0 (-5.6, 7.6)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	682	67.9 (34.2)	57.6 (36.5)	10.3 (5.0, 15.6)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	744	62.2 (35.4)	57.9 (33.5)	4.3 (-0.7, 9.3)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	877	57.9 (36.6)	60.1 (34.9)	-2.2 (-6.9, 2.5)
1 (Donovan 2023, ProtecT)	12-year	Overall	502	55.3 (38.5)	63.5 (37.4)	-8.2 (-14.9, -1.5)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Sexual function - Erections firm enough for intercourse

Table 9. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***sexual function: EPIC item - Erections firm enough for intercourse*** *(at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC item – Erections firm enough for intercourse***		
				Active surveillance *Absolute risk per 1000*	***Definitive treatment*** *Absolute risk per 1000*	***Crude risk ratio*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(crude risk ratio >1 favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	699	494.2	145.7	3.4 (2.6, 4.5)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	770	470.9	191.3	2.5 (2.0, 3.1)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	913	296.5	164.9	1.8 (1.4, 2.3)
1 (Donovan 2023, ProtecT)	12-year	Overall	735	168.5	126.6	1.3 (0.9, 1.9)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(crude risk ratio >1 favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	693	494.2	376.1	1.3 (1.1, 1.6)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	766	470.9	340.2	1.4 (1.2, 1.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	908	296.5	274.1	1.1 (0.9, 1.3)
1 (Donovan 2023, ProtecT)	12-year	Overall	723	168.5	147.1	1.1 (0.8, 1.6)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen

Sexual activity

Table 10. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***sexual activity: QLQ-PR25 sexual activity sub-scale score*** *(range: 0 (most affected) – 100 (least affected) at 1 and 2 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***QLQ-PR25 sexual activity sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Weigel 2021, PREFERE)	1-year	Overall	177	54.1 (23.3)	48.8 (21.1)	5.3 (-2.3, 12.9)
1 (Weigel 2021, PREFERE)	2-year	Overall	177	50.9 (38.9)	43.2 (36.4)	7.7 (-5.2, 20.6)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

2.4.5 Bowel quality of life, bother, and function

Overall bowel function and quality of life

Table 11. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***bowel quality of life: EPIC bowel summary score*** *(range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC bowel summary score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	721	93.4 (8.6)	94.0 (7.7)	-0.6 (-1.8, 0.6)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	800	93.2 (9.4)	93.8 (8.2)	-0.6 (-1.8, 0.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	920	93.0 (9.8)	93.2 (8.7)	-0.2 (-1.4, 1.0)

1 (Donovan 2023, ProtecT)	12-year	Overall	522	92.1 (10.3)	93.1 (8.6)	-1.0 (-2.6, 0.6)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	716	93.4 (8.6)	90.5 (12.2)	2.9 (1.4, 4.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	785	93.2 (9.4)	89.3 (12.8)	3.9 (2.3, 5.5)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	923	93.0 (9.8)	91.2 (10.9)	1.8 (0.5, 3.1)
1 (Donovan 2023, ProtecT)	12-year	Overall	526	92.1 (10.3)	90.6 (10.6)	1.5 (-0.3, 3.3)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Bowel bother

Table 12. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of **bowel bother: EPIC bowel bother sub-scale score** (range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC bowel bother sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
***Active surveillance** with PSA monitoring vs immediate **radical prostatectomy** (positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	722	94.7 (10.4)	95.2 (9.1)	-0.5 (-1.9, 0.9)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	800	94.2 (11.7)	95.1 (9.4)	-0.9 (-2.4, 0.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	925	93.7 (11.6)	94.2 (10.8)	-0.5 (-1.9, 0.9)
1 (Donovan 2023, ProtecT)	12-year	Overall	522	92.5 (13.2)	94.1 (10.1)	-1.6 (-3.6, 0.4)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	717	94.7 (10.4)	90.7 (14.9)	4.0 (2.1, 5.9)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	789	94.2 (11.7)	89.2 (16.7)	5.0 (3.0, 7.0)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	932	93.7 (11.6)	91.7 (13.7)	2.0 (0.4, 3.6)
1 (Donovan 2023, ProtecT)	12-year	Overall	526	92.5 (13.2)	91.0 (13.5)	1.5 (-0.8, 3.8)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Bowel function - Fecal leakage once per week or more

Table 13. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***bowel function: EPIC item - Fecal leakage once per week or more*** *(at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC item - Fecal leakage once per week or more***		
				Active surveillance *Absolute risk per 1000*	***Definitive treatment*** *Absolute risk per 1000*	***Crude risk ratio*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(crude risk ratio <1 favours active surveillance)*						
1 (Donovan 2023 & 2016, ProtecT)	1-year	Overall	722	27.9	19.2	1.5 (0.6, 3.8)
1 (Donovan 2023 & 2016, ProtecT)	2-year	Overall	802	48.1	36.9	1.3 (0.7, 2.5)
1 (Donovan 2023 & 2016, ProtecT)	6-year	Overall	930	49.8	40.6	1.2 (0.7, 2.2)
1 (Donovan 2023, ProtecT)	12-year	Overall	526	57.0	64.6	0.9 (0.5, 1.7)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(crude risk ratio <1 favours active surveillance)*						
1 (Donovan 2023 & 2016, ProtecT)	1-year	Overall	716	27.9	111.7	0.3 (0.1, 0.5)
1 (Donovan 2023 & 2016, ProtecT)	2-year	Overall	788	48.1	99.2	0.5 (0.3, 0.8)
1 (Donovan 2023 & 2016, ProtecT)	6-year	Overall	927	49.8	98.9	0.5 (0.3, 0.8)
1 (Donovan 2023, ProtecT)	12-year	Overall	529	57.0	120.3	0.5 (0.3, 0.9)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen

2.4.6 Urinary quality of life, bother, and function

Overall urinary function and quality of life

Table 14. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***urinary quality of life: EPIC urinary summary score*** *(range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC urinary summary score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	721	91.2 (10.1)	86.5 (13.2)	4.7 (3.0, 6.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	794	90.3 (10.9)	88.1 (12.3)	2.2 (0.6, 3.8)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	909	89.0 (12.5)	88.7 (11.3)	0.3 (-1.3, 1.9)
1 (Donovan 2023, ProtecT)	12-year	Overall	518	88.0 (12.8)	87.1 (13.6)	0.9 (-1.4, 3.2)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	715	91.2 (10.1)	91.9 (9.0)	-0.7 (-2.1, 0.7)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	785	90.3 (10.9)	91.4 (9.8)	-1.1 (-2.6, 0.4)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	906	89.0 (12.5)	91.4 (9.2)	-2.4 (-3.8, -1.0)
1 (Donovan 2023, ProtecT)	12-year	Overall	523	88.0 (12.8)	89.5 (10.2)	-1.5 (-3.5, 0.5)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Urinary bother

Table 15. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***urinary bother: EPIC urinary bother sub-scale score*** *(range: 0 (most affected) – 100 (least affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC urinary bother sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	722	90.0 (12.2)	87.7 (14.1)	2.3 (0.4, 4.2)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	790	88.6 (13.5)	89.0 (13.8)	-0.4 (-2.3, 1.5)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	910	88.0 (13.9)	89.7 (11.9)	-1.7 (-3.4, -0.0)
1 (Donovan 2023, ProtecT)	12-year	Overall	519	86.8 (14.5)	88.6 (14.2)	-1.8 (-4.3, -0.7)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	715	90.0 (12.2)	90.6 (11.0)	-0.6 (-2.3, 1.1)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	781	88.6 (13.5)	90.3 (11.8)	-1.7 (-3.5, 0.1)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	909	88.0 (13.9)	90.3 (11.2)	-2.3 (-3.9, -0.7)
1 (Donovan 2023, ProtecT)	12-year	Overall	524	86.8 (14.5)	88.2 (12.2)	-1.4 (-3.7, 0.9)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

Urinary function – Used one or more pads per day in past 4 weeks

Table 16. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***urinary function: EPIC item - One or more pads per day in past 4 weeks*** *(at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***EPIC item – One or more pads per day in past 4 weeks***		
				Active surveillance *Absolute risk per 1000*	***Definitive treatment*** *Absolute risk per 1000*	***Crude risk ratio*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(crude risk ratio <1 favours active surveillance)*						

1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	722	41.8	261.7	0.2 (0.1, 0.3)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	792	38.3	200.0	0.2 (0.1, 0.3)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	908	83.9	173.6	0.5 (0.3, 0.7)
1 (Donovan 2023, ProtecT)	12-year	Overall	754	114.1	235.8	0.5 (0.4, 0.7)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (crude risk ratio <1 favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	717	41.8	36.3	1.2 (0.6, 2.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	786	38.3	40.6	0.9 (0.5, 1.9)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	905	83.9	35.4	2.4 (1.3, 4.2)
1 (Donovan 2023, ProtecT)	12-year	Overall	747	114.1	76.5	1.5 (1.0, 2.3)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen

2.4.7 Overall cancer-related quality of life

Table 17. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of **cancer-related quality of life: QLQ-C30 global health scale** (range: 0 (most affected) – 100 (least affected) at 1, 2, 5 and 10 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***QLQ-C30 global health scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
***Active surveillance** with PSA monitoring vs immediate **radical prostatectomy** (positive mean difference favours active surveillance)*						
1 (Weigel 2021, PREFERE)	1-year	Overall	177	75.9 (20.2)^	75.6 (21.6)^	0.3 (-6.6, 7.2)
1 (Weigel 2021, PREFERE)	2-year	Overall	177	72.7 (30.3)^	75.2 (30.7)^	-2.5 (-12.7, 7.7)
1 (Donovan **2023** & 2016, ProtecT)	5-year	Overall	781	76.8* (17.6)	78.4 (17.7)	-1.6 (-4.1, 0.9)
1 (Donovan 2023, ProtecT)	10-year	Overall	674	77.2 (17.3)	77.0 (17.5)	0.2 (-2.4, 2.8)
***Active surveillance** with PSA monitoring vs immediate **EBRT** (positive mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	5-year	Overall	794	76.8 (17.6)	77.4 (19.0)	-0.6 (-3.2, 2.0)

1 (Donovan 2023, ProtecT)	10-year	Overall	675	77.2 (17.3)	76.2 (18.8)	1.0 (-1.7, 3.7)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation
^ calculated by technical team from Figure 4a in Weigel 2021 using tools available at https://www.graphreader.com/

2.4.8 Anxiety

Table 18. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***anxiety: HADS Anxiety sub-scale score*** *(range: 0 (least affected) – 21 (most affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***HADS Anxiety sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(negative mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	953	4.0 (3.6)	3.6 (3.6)	0.4 (-0.1, 0.9)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	942	3.9 (3.6)	3.6 (3.4)	0.3 (-0.1, 0.7)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	923	4.1 (3.9)	3.7 (3.5)	0.4 (-0.1, 0.9)
1 (Donovan 2023, ProtecT)	12-year	Overall	507	3.7 (3.5)	3.6 (3.5)	0.1 (-0.5, 0.7)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(negative mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	951	4.0 (3.6)	3.7 (3.6)	0.3 (-0.2, 0.8)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	937	3.9 (3.6)	3.7 (3.4)	0.2 (-0.2, 0.6)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	923	4.1 (3.9)	3.4 (3.2)	0.7 (0.2, 1.2)
1 (Donovan 2023, ProtecT)	12-year	Overall	516	3.7 (3.5)	4.0 (3.7)	-0.3 (-0.9, 0.3)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

2.4.9 Depression

Table 19. *Results of randomised controlled trials comparing active surveillance with immediate definitive treatment for the outcome of* ***Depression sub-scale score*** *(range: 0 (least affected) – 21 (most affected) at 1, 2, 6 and 12 years)*

Studies (N)	***Follow-up***	***Population***	***Participants (N)***	***HADs depression sub-scale score***		
				Active surveillance *Mean (SD)*	***Definitive treatment*** *Mean (SD)*	***Mean difference*** *(95% CI)*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy*** *(negative mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	958	2.4 (2.9)	2.4 (2.9)	0.0 (-0.4, 0.4)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	953	2.6 (3.0)	2.5 (2.7)	0.1 (-0.3, 0.5)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	923	3.1 (3.4)	2.7 (3.1)	0.4 (0.0, 0.8)
1 (Donovan 2023, ProtecT)	12-year	Overall	505	3.1 (3.3)	3.0 (3.2)	0.1 (-0.5, 0.7)
Active surveillance *with PSA monitoring vs immediate* ***EBRT*** *(negative mean difference favours active surveillance)*						
1 (Donovan **2023** & 2016, ProtecT)	1-year	Overall	952	2.4 (2.9)	2.5 (2.7)	-0.1 (-0.5, 0.3)
1 (Donovan **2023** & 2016, ProtecT)	2-year	Overall	943	2.6 (3.0)	2.6 (2.9)	0.0 (-0.4, 0.4)
1 (Donovan **2023** & 2016, ProtecT)	6-year	Overall	928	3.1 (3.4)	2.7 (2.9)	0.4 (0.0, 0.8)
1 (Donovan 2023, ProtecT)	12-year	Overall	513	3.1 (3.3)	3.6 (3.5)	-0.5 (-1.1, 0.1)

CI = confidence interval; EBRT = external beam radiotherapy; N = number; PSA = prostate-specific antigen; SD = standard deviation

2.5 Risk of bias

The results of the risk of bias assessments for the included randomised controlled trials are shown in Figure 2.

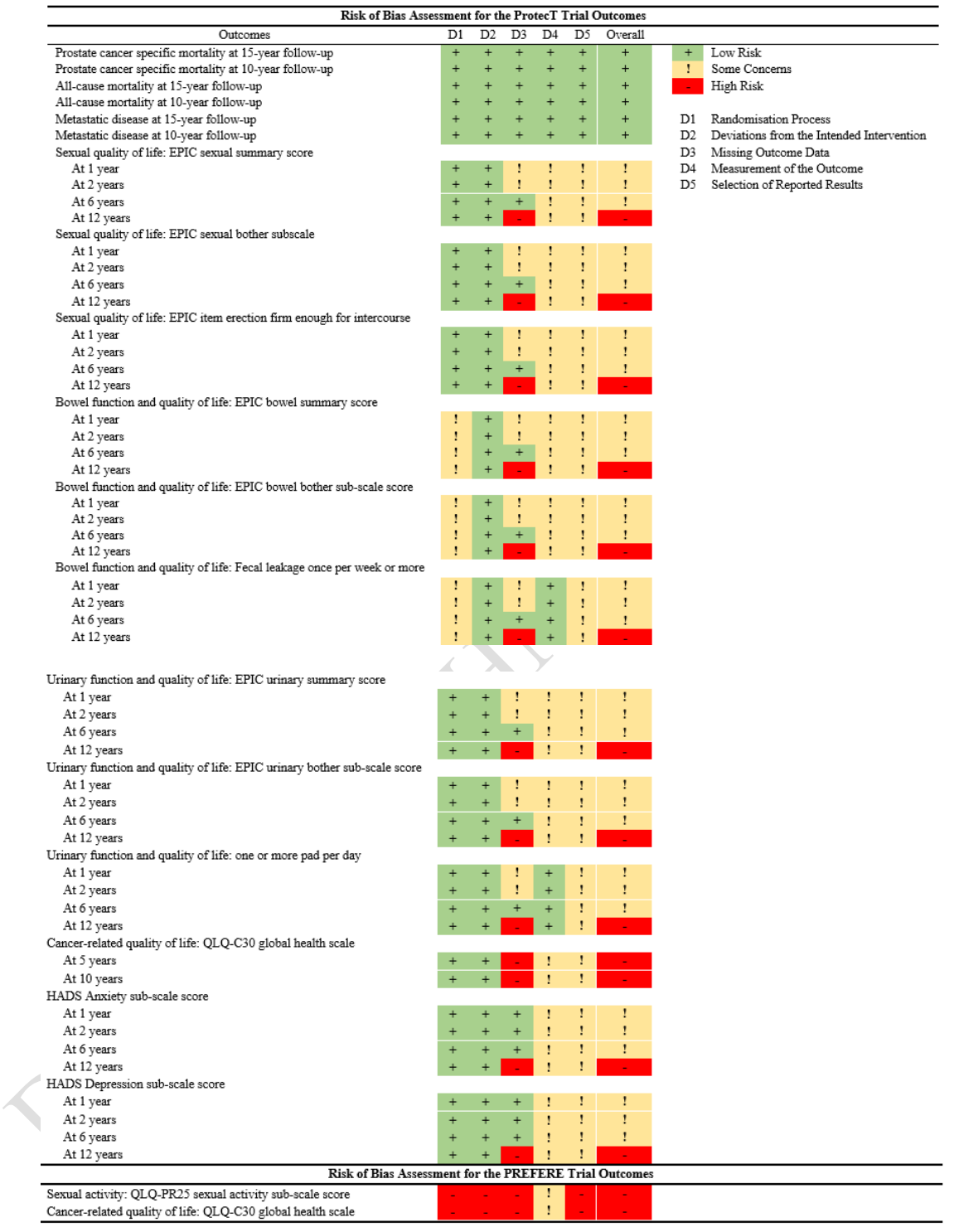

Figure 2. *Risk of bias assessments for included randomised controlled trials using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) (Sterne 2019)*

Key to overall rating
Low risk of bias: "Low" for all domains
Some concerns regarding risk of bias: "Some concerns" but not "high" one or more domains
High risk of bias: "High" for one or more domains

3. GRADE assessment of the certainty of the evidence

Results for 56 important outcomes were extracted. Of these outcomes, 11 were considered critical by the Active Surveillance Working Group. Assessments of the certainty of the evidence for each critical outcome are shown in the tables below.

Prostate cancer-specific mortality (median 15-year follow-up) – assessments are shown in Table 20

All-cause mortality (median 15-year follow-up) – assessments are shown in Table 21

Metastatic disease (median 15-year follow-up) – assessments are shown in Table 22

Sexual quality of life (2-year follow-up) - assessments are shown in Table 23

Sexual bother (2-year follow-up) - assessments are shown in Table 24

Bowel quality of life (2-year follow-up) - assessments are shown in Table 25

Bowel bother (2-year follow-up) - assessments are shown in Table 26

Urinary quality of life (2-year follow-up) - assessments are shown in Table 27

Urinary bother (2-year follow-up) - assessments are shown in Table 28

Overall / cancer-related quality of life (2-year follow-up) - assessments are shown in Table 29

Anxiety (2-year follow-up) - assessments are shown in Table 30

Table 20. *GRADE assessment of the certainty of the evidence for the outcome of* ***prostate cancer-specific mortality (median 15-year follow-up)*** *from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy***			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, outcome was ascertained by trained researchers after reviewing medical records of deceased participants, anonymised, and then reviewed by an independent endpoint committee who were masked to trial assignments. Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***VERY LOW***

Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Very serious concerns	Based on a hazard ratio of 1.52 with 95% confidence interval of 0.72 to 3.22, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 11 more (6 fewer to 47 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was not clinically important, and the 95%CI crossed thresholds for a clinically important increase (small) and for a moderate increase.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, outcome was ascertained by trained researchers after reviewing medical records of deceased participants, anonymised, and then reviewed by an independent endpoint committee who were masked to trial assignments. Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Very serious concerns	Single trial reporting a hazard ratio of 1.14 with 95% confidence interval of 0.57 to 2.72. Based on a hazard ratio of 1.14 with 95% confidence interval of 0.57 to 2.72, in a population of 1000 men with localised prostate cancer undergoing active surveillance, using PSA testing only rather than radiotherapy is estimated to result in 4 more (13 fewer to 36 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was not clinically important, and the 95%CI crossed thresholds for a small clinically important increase and for a moderate increase.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 21. *GRADE assessment of the certainty of the evidence for the outcome of* ***all-cause mortality (median 15-year follow-up)*** *from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	*Rating*	*Reason for rating*	*Certainty of evidence*
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy***			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, outcome was ascertained by reviewing death certificate. Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Extremely serious concerns	Based on a hazard ratio of 1.12 with 95% confidence interval of 0.87 to 1.45, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 22 more (25 fewer to 80 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was clinically important (small increase), but the 95%CI crossed the thresholds for a clinically important small decrease, no change and a clinical unimportant increase as well as moderate and large increases.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials with planned completion dates before 2023 that had not been terminated early.	
Active surveillance *with PSA monitoring vs immediate* ***EBRT***			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, outcome was ascertained by reviewing death certificate. Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Extremely serious concerns	Based on a hazard ratio of 1.14 with 95% confidence interval of 0.88 to 1.47, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than radiotherapy is estimated to result in 26 more (23 fewer to 83 more) prostate cancer deaths at 15 years follow-up. Using a MCID of 15 deaths/1000 at 15 years of follow-up and thresholds for moderate and large effects of 30 deaths/1000 and 60 deaths/1000, the effect estimate was clinically important (small increase), but the 95%CI crossed the thresholds for a small decrease, no difference and a clinically unimportant increase as well as moderate and large increases.	

Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early. .	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 22. *GRADE assessment of the certainty of the evidence for the outcome of* ***metastatic disease (median 15-year follow-up)*** *from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy***			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, metastases were confirmed on imaging or a PSA level of ≥100 ng/mL (considered objective outcomes in this context). Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a hazard ratio of 2.13 with 95% confidence interval of 1.32 to 3.45, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than prostatectomy is estimated to result in 51 more (15 to 106 more) men diagnosed with metastatic prostate cancer at 15 years follow-up. Using a MCID of 30 diagnoses of metastatic disease /1000 at 15 years of follow-up and thresholds for moderate and large effects of 60/1000 and 120/1000, the effect estimate was clinically important (moderate increase), but the 95%CI crossed the threshold for a clinically important small increase/clinically unimportant increase.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	
Active surveillance *with PSA monitoring vs immediate* ***EBRT***			
Risk of bias	No serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and there were no meaningful differences at baseline among the three randomised groups. The risk of bias due to deviations from intended interventions was low. The follow-up was complete for 98% of the participants. The clinicians and patients were unblinded to the group assignment, however, metastases were confirmed on imaging or a PSA level of ≥100 ng/mL (considered objective outcomes in this context). Analysis plan was changed during the course of the trial, but reason given for changing the plan is reasonable.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between	

		1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a hazard ratio of 2.08 with 95% confidence interval of 1.30 to 3.33, in a population of 1000 men with localised prostate cancer undergoing active surveillance using PSA testing only rather than radiotherapy is estimated to result in 51 more (14 to 106 more) men diagnosed with metastatic prostate cancer at 15 years follow-up. Using a MCID of 30 diagnoses of metastatic disease /1000 at 15 years of follow-up and thresholds for moderate and large effects of 60/1000 and 120/1000, the effect estimate was clinically important (moderate increase), but the 95%CI crossed the threshold for a clinically important small increase/clinically unimportant increase.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 23. *GRADE assessment of the certainty of the evidence for the outcome of **sexual quality of life (EPIC sexual summary score at 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 69% of the participants with 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a mean increase in score of 14.8 with 95% confidence interval of 11.2 to 18.3 and using a MCID of a mean difference of 11.6 and mean difference thresholds for moderate and large effects of 23.2 and 46.4, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 69% of the participants with 2-year follow-up. The clinicians and patients were unblinded to the group assignment	***LOW***

		and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean increase in score of 4.8 with 95% confidence interval of 1.0 to 8.6 and using a MCID of a mean difference of 11.6 and mean difference thresholds for moderate and large effects of 23.2 and 46.4, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 24. *GRADE assessment of the certainty of the evidence for the outcome of **sexual bother (EPIC sexual bother subscale at 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 69% of the participants with 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a mean increase in score of 15.2 with 95% confidence interval of 10.3 to 20.1 and using a MCID of a mean difference of 14.8 and mean difference thresholds for moderate and large effects of 29.6 and 59.2, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline	***LOW***

		information was not available for all the participants at the time of randomisation. The follow-up was complete for 69% of the participants with 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean increase in score of 4.3 with 95% confidence interval of 0.7 less to 9.3 more and using a MCID of a mean difference of 14.8 and mean difference thresholds for moderate and large effects of 29.6 and 59.2, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 25. *GRADE assessment of the certainty of the evidence for the outcome of* ***bowel quality of life (EPIC bowel summary score at 2-year follow-up)*** *from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy***			
Risk of bias	Serious concerns	For a single trial reporting this outcome, there were some concerns with the process of randomisation due to baseline differences between the three study groups. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean decrease in score of 0.6 with 95% confidence interval of 1.8 less to 0.6 more and using a MCID of a mean difference of 4.1 and mean difference thresholds for moderate and large effects of 8.2 and 16.4, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance *with PSA monitoring vs immediate* ***EBRT***			

Risk of bias	Serious concerns	For a single trial reporting this outcome, there were some concerns with the process of randomisation due to baseline differences between the three study groups. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	*For 2-year follow-up:* Single trial reporting a mean difference of 3.9 with 95% confidence interval of 2.3 to 5.5. Imprecision was rated to be a serious concern due to the lack of clinically important change in the outcome. Based on a mean increase in score of 3.9 with 95% confidence interval of 2.3 to 5.5 and using a MCID of a mean difference of 4.1 and mean difference thresholds for moderate and large effects of 8.2 and 16.4, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 26. *GRADE assessment of the certainty of the evidence for the outcome of* ***bowel bother (EPIC bowel bother sub-scale score at 2-year follow-up)*** *from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy***			
Risk of bias	Serious concerns	For a single trial reporting this outcome, there were some concerns with the process of randomisation due to baseline differences between the three study groups. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 73% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean decrease in score of 0.9 with 95% confidence interval of 2.4 less to 0.6 more and using a MCID of a mean difference of 4.9 and mean difference thresholds for moderate and large effects of 9.8 and 19.6, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	

Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance *with PSA monitoring vs immediate* ***EBRT***			
Risk of bias	Serious concerns	For a single trial reporting this outcome, there were some concerns with the process of randomisation due to baseline differences between the three study groups. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 73% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***VERY LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	Serious concerns	Based on a mean increase in score of 5.0 with 95% confidence interval of 3.0 to 7.0 and using a MCID of a mean difference of 4.9 and mean difference thresholds for moderate and large effects of 9.8 and 19.6, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 27. *GRADE assessment of the certainty of the evidence for the outcome of* ***urinary quality of life (EPIC urinary summary score at 2-year follow-up)*** *from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy***			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean increase in score of 2.2 with 95% confidence interval of 0.6 to 3.8 and using a MCID of a mean difference of 4.5 and mean difference thresholds for moderate and large effects of 9.0 and 18.0, the 95%CI did not cross any thresholds.	

Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	*For 2-year follow-up:* Single trial reporting a mean difference of -1.1 with 95% confidence interval of -2.6 to 0.4. Imprecision was rated to be a serious concern as the confidence interval crosses the null effect (0). Based on a mean decrease in score of 1.1 with 95% confidence interval of 2.6 less to 0.4 more and using a MCID of a mean difference of 4.5 and mean difference thresholds for moderate and large effects of 9.0 and 18.0, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 28. *GRADE assessment of the certainty of the evidence for the outcome of **urinary bother (EPIC urinary bother sub-score at 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between	

		1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean decrease in score of 0.4 with 95% confidence interval of 2.3 less to 1.5 more and using a MCID of a mean difference of 5.8 and mean difference thresholds for moderate and large effects of 11.6 and 23.2, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	
Active surveillance *with PSA monitoring vs immediate* ***EBRT***			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The outcome measure was added during the trial and hence baseline information was not available for all the participants at the time of randomisation. The follow-up was complete for 72% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the trial and the baseline measures were not included as covariates according to the planned analysis because EPIC scores were not available for men who were recruited early in the trial.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean decrease in score of 1.7 with 95% confidence interval of 3.5 less to 0.1 more and using a MCID of a mean difference of 5.8 and mean difference thresholds for moderate and large effects of 11.6 and 23.2, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 29. *GRADE assessment of the certainty of the evidence for the outcome of* ***cancer-related quality of life (QLQ-C30 score at 2-year follow-up)*** *from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance *with PSA monitoring vs immediate* ***radical prostatectomy***			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be high for the process of randomisation as patients could exclude up to two choices from four possible study arms. There was no information provided on methods of randomisation and allocation concealment. Baseline differences between the trial arms were not reported as the trial was prematurely closed due to poor recruitment. The risk of bias due to deviations from intended interventions, missing outcome data and selection of reported results were also judged to be high as the trial was prematurely closed due to poor recruitment.	***LOW***
Indirectness	No serious concerns	The population, intervention, comparator and outcomes of this trial were relevant.	

Imprecision	Serious concerns	Based on a mean decrease in score of 2.5 with 95% confidence interval of 12.7 less to 7.7 more and using a MCID of a mean difference of 11.6 and mean difference thresholds for moderate and large effects of 23.2 and 46.4, the 95%CI crossed one threshold.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 5 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

Table 30. *GRADE assessment of the certainty of the evidence for the outcome of **anxiety (HADS anxiety sub score 2-year follow-up)** from randomised controlled trials comparing active surveillance with immediate definitive treatment.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Active surveillance** with PSA monitoring vs immediate **radical prostatectomy			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The follow-up was complete for 86% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	
Imprecision	No serious concerns	Based on a mean increase in score of 0.3 with 95% confidence interval of 0.1 less to 0.8 more and using a MCID of a mean difference of 1.7 and mean difference thresholds for moderate and large effects of 3.4 and 6.8, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	
Active surveillance** with PSA monitoring vs immediate **EBRT			
Risk of bias	Serious concerns	For a single trial reporting this outcome, risk of bias was judged to be low for the process of randomisation and deviations from intended interventions. The follow-up was complete for 86% of the participants at 2-year follow-up. The clinicians and patients were unblinded to the group assignment and the outcome was self-reported. Analysis plan was changed during the course of the trial and the baseline measures were not included as covariates according to the planned analysis.	***LOW***
Indirectness	Serious concerns	A substantial proportion of participants likely had non-localised disease at baseline - 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Recruitment between 1999-2009 so Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and for some will differ from current practice.	

Imprecision	No serious concerns	Based on a mean increase in score of 0.2 with 95% confidence interval of 0.2 less to 0.6 more and using a MCID of a mean difference of 1.7 and mean difference thresholds for moderate and large effects of 3.4 and 6.8, the 95%CI did not cross any thresholds.	
Inconsistency	Not Assessable	Not assessable due to a single trial.	
Publication bias	Undetected	Could not be assessed using funnel plot as less than 10 trials. Searches of clinical trial registries did not identify any unpublished trials that had started more than 15 years ago that had not been terminated early.	

CI = confidence interval; EBRT = external beam radiation therapy; MCID = minimal clinically important difference; PSA = prostate specific antigen

4. Summary of findings

Table 31. *Summary of findings for active surveillance vs immediate prostatectomy (PICO11a)*

Outcome (MCID)	***Time frame (years)***	***RCTs (N)***	***Participants (N)***	***Study results and measurements***	***Absolute effect estimates***				***Certainty of evidence (GRADE)***	***Plain text summary***
					Metric	***Immediate prostatectomy***	***Active surveillance (95% CI)***	***Difference (95% CI)***		
Active surveillance based only on PSA monitoring										
Prostate cancer-specific deaths (15/1000)	15 (median)	1	1098	HR: 1.52 (0.72, 3.22)	Prostate cancer deaths per 1000	21.7	32.8 (15.7, 68.2)	11 more per 1000 (6 fewer, 47 more)	Very low[3]	We are uncertain as to whether active surveillance results in a clinically **unimportant^** increase in prostate cancer mortality when compared with immediate prostatectomy.
All-cause deaths (15/1000)	15 (median)	1	1098	HR: 1.12 (0.87, 1.45)	Deaths due to any cause per 1000	211.6	233.8 (186.9, 291.6)	22 more (25 fewer, 80 more)	Very low[2]	We are uncertain as to whether active surveillance results in a clinically **important (small)^** increase in mortality when compared with immediate prostatectomy.
Metastatic disease (30/1000)	15 (median)	1	1098	HR: 2.13 (1.32, 3.45)	Metastatic disease per 1000	47.0	97.5 (61.6, 153.0)	51 more (15 more, 106 more)	Low[1]	Active surveillance may result in a clinically **important (small)^^** increase in metastatic prostate cancer diagnoses when compared with immediate prostatectomy.
Sexual quality of life (11.6)*	2	1	757	Measured by: EPIC sexual summary score Scale: 0-100 Higher better	Mean EPIC sexual summary score	33.4 (mean)	49.2 (mean) (44.6, 51.8)	MD:14.8 more (11.2 more, 18.4 more)	Very low[4]	We are uncertain as to whether active surveillance results in a clinically **important (small)*^** increase sexual quality of life when compared with immediate prostatectomy

Sexual bother (14.8)*	2	1	766	Measured by: EPIC sexual bother score Scale: 0-100 Higher better	Mean EPIC sexual bother score	47.0 (mean)	62.2 (mean) (57.0, 67.1)	MD: 15.2 more (10.3 more, 20.1 more)	Very low[4]	We are uncertain as to whether active surveillance results in a clinically **important (small)*^** decrease in sexual bother when compared with prostatectomy
Bowel quality of life (4.1)*	2	1	800	Measured by: EPIC bowel summary score Scale: 0-100 Higher better	Mean EPIC bowel summary score	93.8 (mean)	93.2 (mean) (92.0, 94.4)	MD: 0.6 less (1.8 less, 0.6 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in bowel quality of life when compared with immediate prostatectomy
Bowel bother (4.9)*	2	1	800	Measured by: EPIC bowel bother score Scale: 0-100 Higher better	Mean EPIC bowel bother sub-scale score	95.1 (mean)	94.2 (mean) (92.7, 95.7)	MD: -0.9 less (2.4 less, 0.6 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in bowel bother when compared with immediate prostatectomy
Urinary quality of life (4.5)*	2	1	794	Measured by: EPIC urinary summary score Scale: 0-100 Higher better	Mean EPIC urinary summary score	88.1 (mean)	90.3 (mean) (88.7, 91.9)	MD: 2.2 more (0.6 more, 3.8 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in urinary quality of life when compared with immediate prostatectomy
Urinary bother (5.8)*	2	1	790	Measured by: EPIC urinary bother score Scale: 0-100 Higher better	Mean EPIC urinary bother sub-score	89.0 (mean)	88.6 (mean) (86.7, 90.5)	MD: 0.4 less (2.3 less, 1.5 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in urinary bother when compared with immediate prostatectomy
Anxiety (1.7)*	2	1	942	Measured by: HADS anxiety sub score Scale: 0-21 Lower better	Mean HADS anxiety sub score	3.6 (mean)	3.9 (mean) (3.5, 4.4)	MD: 0.3 more (0.1 less, 0.8 more)	Low[5]	Active may result in a clinically **unimportant*^** difference in anxiety when compared with immediate prostatectomy
Active surveillance included biopsies at 6 months, 12 months and then every 3 years										
Cancer-related quality of life (11.6)**	2	1	177	Measured by: QLQ-C30 score Scale: 0-100 Higher better	Mean QLQ-C30 score	75.3 (mean)	72.8 (mean) (62.6, 83.0)	MD: 2.5 less (12.7 less, 7.7 more)	Low[6]	Active surveillance may result in a clinically **unimportant** *^ difference in cancer-related quality of life when compared with immediate prostatectomy

CI = confidence interval; HADS = hospital anxiety and depression scale; HR = hazard ratio; MCID = minimally important difference; MD = mean difference; N = number; PSA = prostate specific antigen; RCT = randomised controlled trial

** Half the standard deviation of the **baseline** scores for the study for which results reported (Protect Trial)*

*** Half the standard deviation of the **baseline** scores estimated using GraphReader from Figure 4a in Weigel 2021, the study for which results reported*

[1] Downgraded by two levels due to serious concerns re imprecision and indirectness

[2] Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness

[3] Downgraded by three levels due to very serious concerns re imprecision and serious concerns re indirectness

[4] Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision

[5] Downgraded by two levels due to serious concerns re risk of bias and indirectness

[6] Downgraded by two levels due to serious concerns re risk of bias and imprecision

^ Using thresholds of 15, 30 and 60 deaths /1000 for small (minimal clinically important difference), moderate and large effects

^^ Using thresholds of 30, 60 and 120 metastatic disease diagnoses /1000 for small (minimal clinically important difference), moderate and large effects

**^ Using thresholds of MCID (half standard deviation of baseline score), 2 x MCID and 4 x MCID for small (minimal clinically important difference), moderate and large effects*

Table 32. *Summary of findings for active surveillance* ***based only on PSA monitoring*** *vs immediate external beam radiotherapy (PICO11b)*

Outcome (MCID)	***Time frame (years)***	***RCTs (N)***	***Participants (N)***	***Study results and measurements***	***Absolute effect estimates***				***Certainty of evidence (GRADE)***	***Plain text summary***
					Metric	***Immediate EBRT***	***Active surveillance (95% CI)***	***Difference (95% CI)***		
Prostate cancer-specific deaths (15/1000)	15 (median)	1	1090	HR: 1.14 (0.57, 2.27)	Prostate cancer deaths per 1000	29.3	33.3 (16.8, 65.3)	4 more (13 less, 36 more)	Very low[3]	We are uncertain as to whether active surveillance results in a clinically **unimportant^** increase in prostate cancer mortality when compared with immediate radiotherapy.
All-cause deaths (15/1000)	15 (median)	1	1090	HR: 1.14 (0.88, 1.47)	Death due to any cause per 1000	211.0	236.7 (188.2, 294.2)	26 more (23 less, 83 more)	Very low[2]	We are uncertain as to whether active surveillance results in a **clinically important (small)^** increase in mortality when compared with immediate radiotherapy.
Metastatic disease (30/1000)	15 (median)	1	1090	HR: 2.08 (1.30, 3.33)	Metastatic disease per 1000	49.5	100.2 (63.9, 155.5)	51 more (14 more, 106 more)	Low[1]	Active surveillance may result in a clinically **important (small)^^** increase in metastatic prostate cancer diagnoses when compared with immediate radiotherapy.
Sexual quality of life (11.6)*	2	1	740	Measured by: EPIC sexual summary score Scale: 0-100 Higher better	Mean EPIC sexual summary score	43.4 (mean)	48.2 (mean) (44.4, 52.0)	MD: 4.8 more (1.0 more, 8.6 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in sexual quality of life when compared with immediate radiotherapy
Sexual bother (14.8)*	2	1	744	Measured by: EPIC sexual bother score Scale: 0-100 Higher better	Mean EPIC sexual bother score	57.9 (mean)	61.2 (mean) (57.2, 67.2)	MD: 4.3 more (0.7 less, 9.3 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in sexual bother when compared with immediate radiotherapy
Bowel quality of life (4.1)*	2	1	785	Measured by: EPIC bowel summary score Scale: 0-100 Higher better	Mean EPIC bowel summary score	89.3 (mean)	93.2 (mean) (91.6, 94.8)	MD: 3.9 more (2.3 more, 5.5 more)	Very low[4]	We are uncertain as to whether active surveillance results in a clinically **unimportant*^** increase in bowel quality of life when compared with immediate radiotherapy
Bowel bother (4.9)*	2	1	789	Measured by: EPIC bowel bother score Scale: 0-100 Higher better	Mean EPIC bowel bother sub-scale score	89.2 (mean)	94.2 (mean) (92.2, 96.2)	MD: 5.0 more (3.0 more, 7.0 more)	Very low[4]	We are uncertain as to whether active surveillance results in a clinically **important (small)*^** decrease in bowel bother when compared with immediate radiotherapy

Urinary quality of life (4.5)*	2	1	785	Measured by: EPIC urinary summary score Scale: 0-100 Higher better	Mean EPIC urinary summary score	91.4 (mean)	90.3 (mean) (88.8, 91.8)	MD: 1.1 less (2.6 less, 0.4 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in urinary quality of life when compared with immediate radiotherapy
Urinary bother (5.8)*	2	1	781	Measured by: EPIC urinary bother score Scale: 0-100 Higher better	Mean EPIC urinary bother sub-score	90.3 (mean)	88.6 (mean) (86.8, 90.4)	MD: 1.7 less (3.5 less, 0.1 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in urinary bother when compared with immediate radiotherapy
Anxiety (1.7)*	2	1	937	Measured by: HADS anxiety sub score Scale: 0-21 Lower better	Mean HADS anxiety sub score	3.7 (mean)	3.9 (mean) (3.5, 4.3)	MD: 0.2 more (0.2 less, 0.6 more)	Low[5]	Active surveillance may result in a clinically **unimportant*^** difference in anxiety when compared with immediate radiotherapy.

CI = confidence interval; EBRT = external beam radiation therapy; HADS = hospital anxiety and depression scale; HR = hazard ratio; MCID = minimally important difference; MD = mean difference; N = number; PSA = prostate specific antigen; RCT = randomised controlled trial

** Half the standard deviation of the **baseline** scores for the study for which results reported (Protect Trial)*

*** Half the standard deviation of the **baseline** scores estimated using GraphReader from Figure 4a in Weigel 2021, the study for which results reported*

[1] Downgraded by two levels due to serious concerns re imprecision and indirectness

[2] Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness

[3]Downgraded by three levels due to very serious concerns re imprecision and serious concerns re indirectness

[4]Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision

[5]Downgraded by two levels due to serious concerns re risk of bias and indirectness

^ Using thresholds of 15, 30 and 60 deaths /1000 for small (minimal clinically important difference), moderate and large effects

^^ Using thresholds of 30, 60 and 120 metastatic disease diagnoses /1000 for small (minimal clinically important difference), moderate and large effects

**^ Using thresholds of MCID (half standard deviation of baseline score), 2 x MCID and 4 x MCID for small (minimal clinically important difference), moderate and large effects*

5. Ongoing clinical trials

One potentially relevant trial protocol was identified by searches of clinical trial registries and literature searches. This trial was terminated as it was not meeting accrual target. No potentially relevant ongoing trials were identified other than those included in this systematic review.

Table 33. *Summary of potentially relevant ongoing or terminated randomised controlled trials comparing active surveillance with radical prostatectomy or radiotherapy.*

Study ID	Study name and location	Start date	Completion date	Status	Population	Intervention	Comparator	Outcomes
NCT00499174 ACTRN12611000027910	Observation or radical treatment in patients with prostate cancer - A phase III study of active surveillance therapy against radical treatment in patients diagnosed with favourable risk prostate cancer (START) Australia, Canada, New Zealand and USA	June 2007	October 2013	Terminated (not meeting accrual target)	Males aged 18 years and older, with histologically confirmed prostate adenocarcinoma classified as favourable risk (localised, Gleason score ≤ 6 and PSA ≤ 10 ng/ml) diagnosed within 6 months of randomisation. No previous treatment for prostate cancer including surgery, radiotherapy or androgen deprivation therapy for greater than 3 months.	Active surveillance	Radical prostatectomy or radiotherapy based on patient and physician preference within 90 days of randomisation	Disease-specific survival Overall survival Distant disease-free survival Quality of life anxiety

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Schünemann H, Brozek J, Guyatt G, Oxman A eds. Handbook for grading the quality of evidence and the strength of recommendation using the GRADE approach. Updated October 2013.

Schünemann HJ, Neumann I, Hultcrantz M et al. GRADE guidance 35: Update on rating imprecision for assessing contextualized certainty of evidence and making decisions. J. Clin. Epidemiol. 2022; 150:225-242.

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Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

Umbehr MH, Bachmann LM, Poyet C, et al. The German version of the Expanded Prostate Cancer Index Composite (EPIC): translation, validation and minimal important difference estimation. Health and Quality Outcomes. 2018; 16:36.

Wiegel T, Albers P, Bartkowiak D, Bussar-Maatz R, Harter M, Kristiansen G, et al. Results of a randomized trial of treatment modalities in patients with low or early-intermediate risk prostate cancer (PREFERE trial). Journal of Cancer Research and Clinical Oncology. 2021;147(1):235-42.

APPENDICES

Appendix A:

A.1 Search strategies used for the 2016 guidelines

Database: Medline

#	*Search terms*
1	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 or 2
4	randomized controlled trial.pt.
5	controlled clinical trial.pt.
6	placebo.ab.
7	randomi?ed.ab.
8	randomly.ab.
9	trial.ab.
10	groups.ab.
11	4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp animals/ not humans.sh.
13	11 not 12
14	(active adj2 surveillance).mp
15	(expectant$ adj2 (management or treat$)).mp
16	delay$ intervention.mp
17	(active adj1 monitoring).tw
18	'active monitoring'.tw
19	'conservative monitoring'.tw
20	'delayed treatment$'.tw
21	'watchful observation'.tw
22	'watchful surveillance'.tw
23	'watchful monitoring'.tw
24	'expectant monitoring'.tw
25	'expectant surveillance'.tw
26	'delayed therap$'.tw
27	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	3 AND 13 AND 27

Used the Cochrane sensitivity maximizing filters for identifying randomised controlled trials (http://handbook.cochrane.org, accessed 20/02/2013/ Centre for Reviews and Dissemination systematic review/ meta-analyses strategy 2 (Lee et al, (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology 12:51)

Search terms used to identify Aboriginal and Torres Strait Islander populations

#	*Search terms*
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab
2	(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or metast$ or adeno$)).mp.
3	prostate cancer.mp. or exp Prostatic Neoplasms/
4	1 AND (2 OR 3)

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

Database: Embase

#	Search terms
1	'prostate cancer'/exp OR 'prostate cancer'
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR metast* OR adeno*)
3	#1 OR #2
4	active NEAR/2 surveillance
5	expectant* NEAR/2 (management OR treat*)
6	delay* NEAR/3 intervention
7	#4 OR #5 OR #6
8	rct
9	'randomized controlled trial'/exp OR 'randomized controlled trial'
10	'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'randomized controlled trials'/exp OR 'randomized controlled trials' OR 'randomised controlled trials'
11	'random allocation'/exp OR 'random allocation'
12	'randomly allocated'
13	'randomization'/exp OR 'randomization'
14	allocated NEAR/2 random
15	'double blind procedure'/exp OR 'double blind procedure'
16	'single blind procedure'/exp OR 'single blind procedure'
17	single NEXT/1 blind*
18	double NEXT/1 blind*
19	(treble OR triple) NEXT/1 blind*
20	placebo*
21	'placebo'/exp OR 'placebo'
22	'prospective study'/exp OR 'prospective study'
23	'crossover procedure'/exp OR 'crossover procedure'
24	'clinical trial'/exp OR 'clinical trial'
25	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26	#3 AND #7 AND #25

Search terms used to identify Aboriginal and Torres Strait Islander populations

#	Search terms
1	'australia'/exp OR australia*:ab,ti
2	'aborigine'/exp OR aborigin*:ab,ti OR indigenous:de,ab,ti
3	'torres strait islander':ab,ti OR 'torres strait islanders':ab,ti
4	#1 AND #2 OR #3

Databases: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews and Health Technology Assessment database

#	Search terms
1	(prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).tw
2	prostate cancer.mp. or exp Prostatic Neoplasms/
3	1 OR 2

A.2 Search strategy used for the 2025 guidelines update

Databases: Medline, Embase and CENTRAL databases (via Ovid platform)

#	*Search terms*
1	exp Prostatic Neoplasms/
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta*)).tw.
3	1 or 2
4	Watchful Waiting/
5	((active* or watch* or expect* or conservat*) adj2 (surveillan* or monitor* or observat* or wait* or manag*)).tw.
6	((deferr* or delay*) adj2 (treat* or therap*)).tw.
7	4 or 5 or 6
8	3 and 7
9	Prostatic Neoplasms/su
10	exp Prostatectomy/
11	prostatectom*.tw.
12	(radical adj1 (therap* or treat*)).tw.
13	9 or 10 or 11 or 12
14	exp Radiotherapy/
15	radiotherap*.tw.
16	((radiat* or radio*) adj4 (therap* or treat*)).tw.
17	((interstitial* or intracavit* or implant* or surface* or internal* or external* or conform* or seed*) adj4 (irradiat* or radiation* or radio* or therap* or treat*)).tw.
18	(brachytherap* or curietherap*).tw.
19	EBRT.tw.
20	((seed* or permanent*) adj2 implant*).tw.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	13 or 21
23	8 and 22
24	randomized controlled trial.pt.
25	controlled clinical trial.pt.
26	randomi?ed.tw.
27	randomly.tw.
28	trial.tw.
29	RCT*.tw.
30	groups.tw.
31	24 or 25 or 26 or 27 or 28 or 29 or 30
32	23 and 31
33	conference abstract.pt.
34	32 not 33
35	limit 34 to english language
36	limit 35 to yr="2018 -Current"
37	remove duplicates from 36

Used a modified Cochrane sensitivity maximizing filter for identifying randomized controlled trials in Medline (https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies; accessed 28/08/2023).

Appendix B: GRADE assessment of the certainty of the evidence

Grade	*Definition*
⊕⊕⊕⊕ High certainty	We are very confident that the true effect lies close to that of the estimate of the effect.
⊕⊕⊕◯ Moderate certainty	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ Low certainty	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
⊕◯◯◯ Very low certainty	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix C: Excluded studies - 2016 guidelines systematic review

Study	*Reason for Exclusion*
Bastian 2009	Review with inappropriate study design
Bul 2012	Inappropriate study design. Not randomised.
Dahabreh 2012	Inappropriate study design. No appropriate data in paper.
Godtman 2013	Inappropriate study design. Single-arm AS cohort study.
Heidenreich 2011	EAU guidelines. No appropriate data in paper.
Khatami 2006	Inappropriate study design. Not biopsy determined PCa.
Khatami 2009	Biomarker analysis. No appropriate data in paper.
Klotz 2004	Inappropriate study design. No appropriate data in paper.
Klotz 2008	No appropriate data in paper.
Klotz 2010	Inappropriate study design. No appropriate data in paper.
Lane 2010	No appropriate data in paper.
Mhaskar 2012	No appropriate data in paper.
Mullins 2013	Inappropriate study design. No appropriate data in paper.
Roach 2012	Inappropriate study design. Intervention is WW, not AS.
Roemeling 2006	Inappropriate study design. Intervention (WW not AS) not randomised.
Roemeling 2007a (EU)	Inappropriate study design. Intervention not randomised.
Roemeling 2007b (C)	Inappropriate study design
van den Bergh 2010	Inappropriate study design
Wever 2013	Inappropriate study design
Wilt 1994	Inappropriate study design. A RCT with WW as the intervention
Wilt 1995	Inappropriate study design. A RCT with WW as the intervention.
Wilt 1997	No appropriate data in paper.
Wong 2012	Inappropriate study design. No appropriate data in paper.

References of excluded studies – 2016 guidelines

Bastian PJ, Carter BH, Bjartell A, Seitz M, Stanislaus P, Montorsi F et al. Insignificant prostate cancer and active surveillance: from definition to clinical implications. *European Urology* 2009; 55:1321-30.

Bul M, van den Bergh RC, Zhu X, Rannikko A, Vasarainen H, Bangma CH et al. Outcomes of initially expectantly managed patients with low or intermediate risk screen-detected localized prostate cancer. *BJU International* 2012; 110:1672-7.

Dahabreh IJ, Chung M, Balk EM, Yu WW, Mathew P, Lau J, Ip S. Active surveillance in men with localized prostate cancer: a systematic review. *Annals of Internal Medicine.* 2012; 156(8):582-90.

Godtman RA, Holmberg E, Khatami A, Stranne J, Hugosson J. Outcome following active surveillance of men with screen-detected prostate cancer. Results from the Goteborg randomised population-based prostate cancer screening trial. *European Urology* 2013; 63:101-7.

Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *European Urology* 2011; 59:61-71.

Khatami A, Aus G, Damber JE, Lilja H, Lodding P, Hugosson J. PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. *International Journal of Cancer* 2006; 120(1):170-4.

Khatami A, Hugosson J, Wang W, Damber JE: Ki-67 in screen-detected, low-grade, low-stage prostate cancer, relation to prostate-specific antigen doubling time, Gleason score and prostate-specific antigen relapse after radical prostatectomy. *Scandinavian Journal of Urology & Nephrology* 2009; 43:12-8.

Klotz L. Active surveillance with selective delayed intervention: Using natural history to guide treatment in good risk Prostate cancer. *Journal of Urology* 2004; 172:S48–S51.

Klotz L. Active surveillance for prostate cancer: trials and tribulations. *World Journal of Urology* 2008; 26:437-42.

Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort with Localized Prostate Cancer. *Journal of Clinical Oncology* 2010; 28(1):126-31.

Lane JA, Hamdy FC, Martin RM, Turner EL, Neal DE, Donovan JL. Latest results from the UK trials evaluating prostate cancer screening and treatment: the CAP and ProtecT studies. *European Journal of Cancer.* 2010; 46(17):3095-101.

Mhaskar AR, Quinn G, Vadaparampil S,Djulbegovic B, Gwede CK, Kumar A. Timing of first-line cancer treatments - early versus late - a systematic review of phase III randomized trials. *Cancer Treatment Reviews* 2010; 36(8):621-8.

Mullins JK, Bonekamp D, Landis P, Begum H, Partin AW, Epstein JI et al. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. *BJU International* 2013; 111:1037-45.

Roach M III, Thomas K. Overview of randomized controlled treatment trials for clinically localized prostate cancer: implications for active surveillance and the United States preventative task force report on screening? *Journal of the National Cancer Institute Monographs* 2012; 45:221-9.

Roemeling S, Roobol MJ, Postma R, Gosselaar C, van der Kwast TH, Bangma CH et al. Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. *European Urology* 2006; 50:475-82.

Roemeling S, Roobol MJ, de Vries SH, Wolters T, Gosselaar C, van Leenders GJ et al. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. *European Urology* 2007; 1251(51):1244-50.

Roemeling S, Roobol MJ, Kattan MW, van der Kwast TH, Steyerberg EW, Schroder FH. Nomogram use for the prediction of indolent prostate cancer: impact on screen-detected populations. *Cancer* 2007; 110:2218-21.

van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T et al. Swedish and Dutch sections of the European Randomized Study of Screening for Prostate Cancer. Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? *Cancer* 2010; 116:1281-90.

Wever EM, Heijnsdijk EA, Draisma G, Bangma CH, Roobol MJ, Schroder FH et al. Treatment of local-regional prostate cancer detected by PSA screening: benefits and harms according to prognostic factors. *British Journal of Cancer* 2013; 108:1971-7.

Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial: a randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *Journal of Urology* 1994; 152:1910-4.

Wilt TJ, Brawer MK. The Prostate cancer Intervention versus Observation Trial (PIVOT): A randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. *Cancer* 1995; 75:1963-8.

Wilt TJ, Brawer MK. The Prostate Cancer Intervention versus Observation Trial (PIVOT). *Oncology* 1997; 11(8):1133-43.

Wong LM, Neal DE, Johnston RB, Shah N, Sharma N, Warren AY et al. International multicentre study examining selection criteria for active surveillance in men undergoing radical prostatectomy. *British Journal of Cancer* 2012; 107:1467-73.

Appendix D: Excluded studies - 2025 review update

Article	*PMID/DOI*	*Reason for exclusion*
Achard 2021	https://dx.doi.org/10.1159/000513258	Excluded publication type
Ahlberg 2019	https://dx.doi.org/10.1136/bmjopen-2018-027860	Excluded publication type
Albers 2021	https://doi.org/10.1007/s00345-020-03154-7	No comparative data
Bill-Axelson 2018	https://dx.doi.org/10.1056/NEJMoa1807801	No comparator of interest
Bryant 2020	https://dx.doi.org/10.1111/bju.14987	No outcome of interest
Carlsson 2019	https://dx.doi.org/10.1016/j.eururo.2019.03.010	No comparator of interest
Chan 2021	https://dx.doi.org/10.3390/cancers13133274	Systematic review with different inclusion criteria
Dahm 2020	PMID: 32986341	No comparator of interest
Degeling 2021	https://dx.doi.org/10.1016/j.jval.2021.06.004	Excluded publication type
Donovan 2019	https://dx.doi.org/10.1016/j.jclinepi.2019.05.036	Excluded study design
Fenton 2018	https://dx.doi.org/10.1001/jama.2018.3712	Systematic review with different inclusion criteria
Godtman 2018	https://dx.doi.org/10.1016/j.juro.2018.04.078	No population of interest
Hamdy 2020	https://dx.doi.org/10.3310/hta24370	Excluded publication type
Lane 2022	https://dx.doi.org/10.1111/bju.15739	Superseded by more recent publication
Luo 2021	https://dx.doi.org/10.1177/1457496919883962	Systematic review with different inclusion criteria
Neal 2020	https://dx.doi.org/10.1016/j.eururo.2019.10.030	Superseded by more recent publication
Ng 2019	https://dx.doi.org/10.1177/2051415818812316	Systematic review with different inclusion criteria
Nouhi 2019	https://dx.doi.org/10.18502/ijph.v8i4.978	Systematic review with different inclusion criteria
Johansson 2018	https://dx.doi.org/10.1016/j.euo.2018.03.003	No comparator of interest
Thomsen 2019	https://dx.doi.org/10.1016/j.clgc.2019.05.005	Excluded study design
Tiruye 2022	https://dx.doi.org/10.1186/s12894-022-01117-1	Excluded study design
Vernooij 2021	https://doi.org/10.1002/14651858.CD006590.pub3	Systematic review with overlapping inclusion criteria. Included ProtecT trial studies (Hamdy 2016, Donovan 2016) included in this systematic review and superseded by more recent studies.
Wade 2020	https://dx.doi.org/10.1136/bmjopen-2019-036024	No outcome of interest
Wilt 2020	https://dx.doi.org/10.1016/j.eururo.2020.02.009	No comparator of interest

Appendix E: International Society Urological Pathology Gleason Grade Groups:

Group 1 have a Gleason score of ≤ 6 (3+3), associated with low risk of progression;

Group 2 have Gleason score of 7 (3+4), associated with favourable intermediate risk of progression;

Group 3 have a Gleason score of 7 (4+3), associated with intermediate risk of progression;

Groups 4 and 5 have Gleason scores of ≥ 8, associated with high risk of progression.

3.18 Clinical question 11 – Active Surveillance PICO 11C

Clinical question 11: *What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?*

Introduction

For the 2016 guidelines a systematic review was undertaken of randomised controlled trials and non-randomised studies comparing active surveillance with immediate treatment for localised prostate cancer to identify active surveillance protocols with long term outcomes comparable to those for immediate treatment. Three cohort studies were included; no randomised controlled trials were found. The 2016 guidelines did not consider comparisons of different active surveillance protocols. Following the publication of the 2016 guidelines the results of the ProtecT trial were published; a randomised controlled trial comparing active surveillance with immediate treatment. Consequently, to address this clinical question for this guideline update:

- The selection criteria for the update of the systematic review of comparisons of active surveillance with immediate treatment for localised prostate cancer were revised to include randomised controlled trials only, and
- A second systematic review was undertaken to identify randomised controlled trials comparing different active surveillance protocols.

This is the report for the second systematic review.

Systematic review report – Randomised controlled trials comparing active surveillance protocols for individuals diagnosed with localised prostate cancer

Authors

Denise Campbell, Isabel Rewais, Suzanne Hughes

PICO 11C

This systematic review addresses the following PICO which is summarised in detail in Table 1.

PICO 11C. *For individuals with biopsy-diagnosed localised prostate cancer following an active surveillance protocol, which combination of monitoring tests, testing frequency and clinical or other criteria for intervention achieve the best outcomes in terms of length and quality of life?*

Table 35. *PICO components*

Population	*Intervention*	*Comparator*	*Outcomes*	*Study design*
Individuals with biopsy-(histologically) confirmed localised prostate cancer (cT1-2)	Active surveillance	Another active surveillance protocol	All-cause mortality Prostate cancer-specific mortality Metastasis Health-related quality of life Adverse patient-reported outcomes	Randomised controlled trials or systematic reviews thereof

1. Methods

1.1 Selection Criteria

Table 2. *Selection criteria for systematic review of randomised controlled trials comparing different active surveillance protocols for men diagnosed with localised prostate cancer.*

Selection criteria	*Inclusion criteria*	*Exclusion criteria*
Study type	Intervention	Nomograms (or predictive model) that have not been validated in a separate cohort
Study design	Randomised, or pseudo-randomised controlled trial, or meta-analysis/systematic review thereof	Cohort studies
Population	Individuals with biopsy (histologically) confirmed localised (cT1-2) prostate cancer Or Subgroups thereof	Studies that restricted participants based on biomarker status More than 10% > cT2 prostate cancer
Intervention	Active surveillance – monitored for disease progression and offered definitive/curative therapy, i.e., prostatectomy or radiotherapy (external beam radiation therapy or brachytherapy) if progression evident	Watchful waiting (men not necessarily offered definitive/curative therapy if disease progresses rather offered treatments to manage symptoms)
Comparator	Another active surveillance protocol	
Outcome	All-cause mortality Prostate cancer-specific mortality Metastasis (nodal and/or distant) Overall health-related quality of life Adverse patient reported outcomes: Urinary function/bother Sexual function/bother Bowel function/bother Anxiety Depression	Disease progression
Publication date	1st January 1990 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data or systematic review thereof	Conference abstract Editorial Letter or article that does not report original data
Language	English	

1.2 Definitions and terminology

For the purposes of this review:

Localised prostate cancer refers to cancer that is confined within the prostate, classified as clinical stage <T3 (Bruinsma 2017)

Active surveillance is a monitoring strategy for men with clinically localised prostate cancer. It aims to minimise treatment-related toxicity without compromising survival by achieving correct timing for curative treatment for those who may eventually require it.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in August 2023:

- American College of Preventive Medicine website
- American College of Radiology website
- American Cancer Society website
- American Urology Association website
- Agency for Healthcare Research and Quality website

- American Society of Clinical Oncology website
- Alberta Health Services website
- Association Francaise d'Urologie website
- BIGG international database of GRADE guidelines database
- British Columbia Guidelines website
- Canadian Urology Association website
- Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines website
- Cancer Care Ontario website
- Cancer Society NZ website
- Danish Urological (Prostate) Cancer Group (DAPROCA) website
- European Association of Urology (EAU) website
- European Society for Medical Oncology (ESMO) website
- European Society for Therapeutic Radiology and Oncology (ESTRO) website
- Guidelines International Network (GIN) database
- International Health Technology Assessment (HTA) database
- International Society of Geriatric Oncology website
- Japanese Urological Association website
- Leitlinienprogramm Onkologie website
- Memorial Sloan Kettering Cancer Center (MSKCC)
- Ministry of Health New Zealand website
- NHS website
- National Institute for Health and Care Excellence (NICE) Guidelines website
- National Cancer Control Programme (NCCP) website
- National Comprehensive Cancer Network (NCCN) website
- Prostate Cancer UK website
- Royal Australian College of General Practitioners (RACGP) website
- Royal College of Pathologists of Australasian (RCPA) website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- UK National Screening Committee website
- US Preventive Services Task Force website
- *Urological Society of Australia and New Zealand (USANZ) website*
- World Health Organisation website

To be considered for adoption by the Working Party, guidelines had to address the clinical question of interest, meet NHMRC requirements and standards (https://www.nhmrc.gov.au/guidelinesforguidelines), i.e., be based on a systematic review of the evidence and demonstrate a transparent link between the systematic review of the evidence and the recommendations, and be published from 2023 onwards so as to include recent published results. Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence i.e., did not report using systematic methods to search for evidence, did not clearly

describe the criteria for selecting the evidence, did not assess the risk of bias (or where this is not possible, appraise the quality of the evidence) or did not undertake a GRADE assessment of the certainty of the evidence, or if the systematic reviews of the evidence were not accessible or were not available in English.

1.4 Literature searches

This systematic review covers literature published from January 1990 onwards. Assessment of existing guidelines identified two systematic reviews that adequately captured relevant literature published from January 1990 to March 2018; a systematic review for the previous guidelines, Clinical practice guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer (CCA & PCFA 2015) and a systematic review for the NICE guideline NG131: Prostate cancer: diagnosis and management (NICE 2019). We assessed their included studies for inclusion in our systematic review, and designed searches to identify randomised controlled trials or systematic reviews thereof published from 2018 onwards.

Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations), Embase and Cochrane CENTRAL databases were searched on 28th August 2023 combining text terms and database-specific subject headings for prostate cancer and active surveillance, and a filter for randomised controlled trials. Searches were limited to articles published in English from 1st January 2018 onwards, with monthly alerts capturing articles published until the final literature cut-off date, 1st September 2024. In addition, the Cochrane Database of Systematic Reviews was searched on 13th March 2024 using the search term "prostate". The searches were designed to identify potentially relevant trials in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used in the search is included as Appendix A. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

Extraction of study characteristics and results were planned. The following study characteristics were to be extracted; country and year of publication, participant eligibility and age, duration of follow-up, active surveillance monitoring protocols and triggers for change to treatment, relevant outcomes reported, subgroup data available, and additional information including notable study limitations. Effect estimates and 95% confidence intervals as reported in the study were to be extracted or calculated using relevant reported data. Pooled analyses were planned where there were two or more studies reporting the same outcome at corresponding time points.

1.6 Risk of bias assessments

Independent assessments of the risk of bias by two reviewers using Cochrane Collaboration Risk of Bias-II tool (Sterne 2019) were planned.

1.7 GRADE assessment of the certainty of the evidence

GRADE assessments were planned to assess the certainty of the body of evidence for each outcome (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence would be rated high, moderate, low or very low based on assessment of risk of bias, indirectness, imprecision, inconsistency or heterogeneity, and publication bias based on guidance from the GRADE Handbook (Schunemann 2013) and Schunemann et al 2022. As per GRADE guidance, randomised controlled trials started with a high level of certainty in the evidence and were to be downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

1.8 Clinical trial registry searches

Potentially relevant ongoing or unpublished trials were identified from literature and clinical trial registry searches. Clinical trial registries were searched for relevant ongoing or unpublished randomised controlled trials registered or posted by 16th September 2024 using the search terms listed below:

Clinicaltrials.gov using the terms:

"prostate cancer" and "surveillance"

"prostate cancer" and "active surveillance"

International Clinical Trials Registry Platform (https://trialsearch.who.int/Default.aspx) using the terms:

"active surveillance" and "prostate cancer"

"radical prostatectomy" and "prostate cancer"

"comparative effectiveness" and "surgery" and "prostate cancer"

"comparative effectiveness" and "radiation therapy" and "prostate cancer"

"radiotherapy" and "prostate cancer"

"prostate cancer" and "active monitoring"

"prostate cancer" and "delayed treatment"

2. Results

2.1 Guidelines searches

No relevant guidelines published from 2023 onwards were identified which were reportedly based on systematic reviews of the literature.

2.2 Literature searches

Figure 1 outlines the process for identifying relevant articles published from 2018 onwards. The combined search of Medline, Embase and CENTRAL databases retrieved 835 records. Titles and abstracts were examined by two reviewers, and 8 articles were retrieved for a more detailed evaluation. The search of the Cochrane Database of Systematic Reviews did not identify any potentially relevant systematic reviews. No randomised studies were found by the searches or by systematic reviews undertaken for the previous 2016 guidelines or the NICE 2019 guidelines that directly answered the clinical question and met the inclusion criteria for this systematic review. As such, there were no studies of Aboriginal and/or Torres Strait Islander peoples that met the inclusion criteria.

The retrieved articles that were not included in this systematic review and the reasons for their exclusion are documented in Appendix B. In summary, the main reason for exclusion was no outcome of interest.

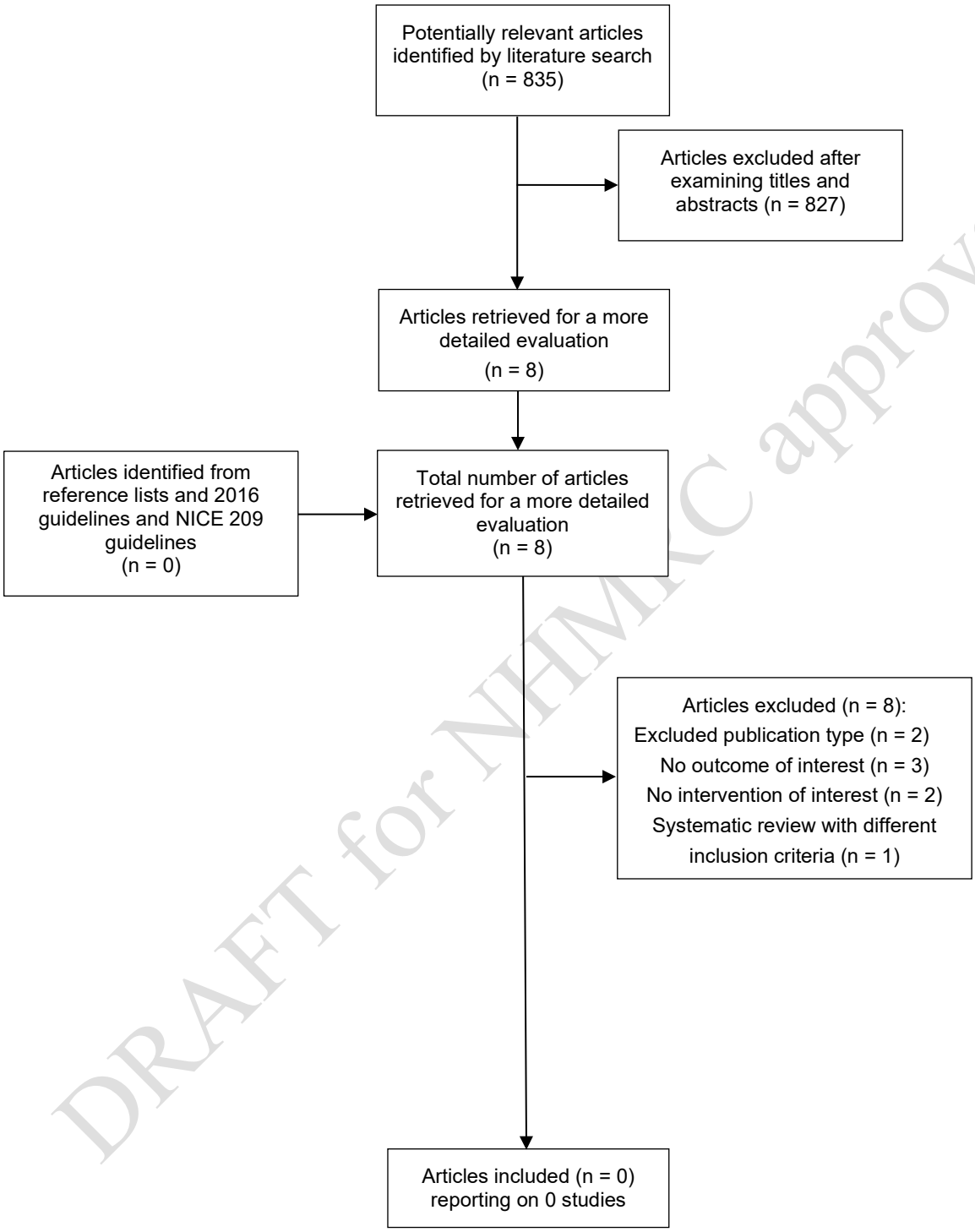

Figure 1. *Process of inclusion and exclusion of articles for the systematic review update.*

3. Ongoing clinical trials

Five potentially relevant ongoing trial protocols were identified by searches of clinical trial registries and literature searches, two of which were terminated early or withdrawn. Two of the three remaining ongoing trials are the PCASTt trial in Scandinavia and in the UK.

Table 3. *Summary of potentially relevant ongoing and terminated randomised controlled trials comparing one active surveillance protocol with another*

Study ID	***Study name, location***	***Start date***	***Planned completion date***	***Status***	***Population***	***Intervention***	***Comparator***	***Outcomes***
NCT01838265	Trial of prostate cancer patients undergoing active surveillance with or without MRI-guided management (MGM) USA	August 2012	August 2018	Withdrawn (unlikely to accrue)	Men aged 35 to 75 years with biopsy-confirmed prostate cancer diagnosed ≤1 year ago Tumour stage ≤ T2a based on DRE and biopsy must consist of at least 8 cores with one or two biopsy cores with less than 50% tumour present in each core and Gleason score ≤ 6 (3+3).	MRI-managed active surveillance – **MRI ultrasound or MRI-guided biopsies** within 6 months of enrollment and at annually thereafter up to 36 months after the initial biopsy (maximum four biopsies).	Active surveillance – **standard TRUS guided biopsies** within 6 months of enrollment and annually thereafter up to 36 months after the initial biopsy (maximum four biopsies).	Rate of progression Expression levels of biomarkers in biopsies Effect of MRI monitoring on health-related Quality of Life
NCT02564549	MRI-based active surveillance to avoid the risks of serial biopsies in men with low-risk prostate cancer USA	October 2015	October 2017	Terminated (study halted prematurely and will not resume)	Men aged ≥ 40 years with biopsy-confirmed prostate cancer diagnosed ≤ 1 year ago PSA < 10 ng/ml Gleason score ≤ 6	**Annual mpMRI** with **targeted biopsy**	**Annual** TRUS-guided **systematic biopsy**	Percentage of patients who remain on active surveillance from the time of randomisation until the end of study participation Rate of biopsy-related infections Rate of missed Gleason score ≥ 4+3 as determined by template biopsy at end of study
NCT02914873	SPCG17: Prostate Cancer Active Surveillance Trigger Trial (PCASTt) Scandinavia (Ahlberg 2019)	October 2016	December 2033	Recruiting	Men with biopsy-confirmed prostate cancer diagnosed ≤1 year ago Tumour stage ≤ T2a, NX, M0 PSA < 15 ng/ml PSA density ≤ 0.2 ng/ml/cc. Gleason score 6 (3+3) or 7 (3+4)	Active surveillance with **standardised triggers** for biopsy and treatment PSA - 6 monthly Annual clinical exam Biennial bp/mpMRI	Active surveillance with **urologist determined triggers** for biopsy and treatment PSA – 6 monthly Annual clinical exam Biennial bp/mpMRI	At median follow-up of 10 years: Progression-free survival Cumulative incidence of pT3 at radical prostatectomy Cumulative incidence of metastases

					Life expectancy >10 years with no upper age limit. Undergone bp/mpMRI with targeted biopsies if PI-RADS 3-5 and systematic biopsy (optional, if the diagnosis is based on MRI with targeted biopsies)	*Triggers for re-biopsy* • PSA density > 0.2 ng/ml/cc – systematic biopsy. • MRI progression – targeted biopsy *Triggers for initiating curative treatment* • MRI progression in lesions with confirmed Gleason pattern 4 • Pathological progression based on Gleason patterns, number of cores and core cancer length	*Triggers for re biopsy* Urologist judgment *Triggers for initiating curative treatment* Urologist judgment	Cumulative number of treatments with curative intent Cumulative incidence of switch to watchful waiting Quality of life Cumulative prostate cancer mortality
NCT04029714	Prostate Cancer Active Surveillance Trigger Trial (PCASTt-UK) UK	September 2019	December	Recruiting	Men with biopsy-confirmed prostate cancer diagnosed ≤1 year ago, tumour stage ≤ T2a, NX, M0 PSA <15 ng/ml PSA density ≤ 0.2 ng/ml/cc. Gleason pattern 6 (3+3) or 7 (3+4, < 3 cores, < 10mm cancer in one core) Life expectancy >10 years with no upper age limit.	Active surveillance with **standardised triggers** for biopsy and treatment PSA - 6 monthly Annual clinical exam Biennial MRI *Triggers for re-biopsy* • PSA density > 0.2 ng/ml/cc – systematic biopsy. • MRI progression – targeted biopsy *Triggers for initiating curative treatment* • MRI progression in lesions with confirmed Gleason pattern 4 • Pathological progression based on Gleason	Active surveillance with **urologist determined triggers** for biopsy and treatment PSA - 6 monthly Annual clinical exam Biennial MRI *Triggers for re-biopsy* Urologist judgment *Triggers for initiating curative treatment* Urologist judgment	At median follow-up of 10 years: Progression-free survival Cumulative incidence of pT3 on radical prostatectomy Cumulative incidence of metastases Cumulative number of treatments with curative intent Cumulative incidence of switch to watchful waiting Quality of life (median 10 years follow- up)

						patterns, number of cores and core cancer length		
NCT06280781	Approaches to Long-Term Active Surveillance of patients with prostate cancer (IP9-ATLAS) UK	July 2024	June 2032	Not yet recruiting	Individuals aged 18 years or above (no upper age limit) with a prostate (either cis-male gender or trans-female gender with no prior androgen deprivation hormone use) with biopsy-confirmed localised prostate cancer diagnosed ≤ 9 months ago who have chosen active surveillance as management option.	Regular **MRI-based** active surveillance PSA – 6 monthly bpMRI annually if visible lesion or medium risk disease bpMRI at year 1 ,3 and 5 if no visible lesion and low risk disease *Re-biopsy* Targeted biopsy if MRI PRECISE score ≥ 4 (radiological progression) Or if a consistent rise in PSA over 3 readings that is concerning for progression.	Active surveillance according to **current NICE guidance** PSA 3 monthly in year 1 and then 6 monthly with rectal exam annually. MRI at 12 months if not had one at diagnosis *Re-biopsy* if changes in rectal exam or PSA.	At follow-up of 5 years: Progression to Grade group ≥3 or intraductal cancer or lymphovascular invasion. Progression to higher stage (≥ T3 or ≥ N or ≥ M1) Cost-effectiveness Biopsies MRI and biopsy-related adverse events Patient treatment options for progressive disease Patient compliance Annual assessments of urinary, erectile and bowel function, anxiety and overall health-related quality of life

bpMRI = biparametric MRIDRE = digital rectal examination; mpMRI = multiparametric MRI; NICE = National Institute for Health and Care Excellence; TRUS = transrectal ultrasound

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APPENDICES

Appendix A: Literature search strategy to identify RCTs published from 2018 onwards

Databases: Medline, Embase and CENTRAL (via Ovid platform)

#	*Search terms*
1	exp Prostatic Neoplasms/
2	(prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta*)).tw.
3	1 or 2
4	Watchful Waiting/
5	((active* or watch* or expect* or conservat*) adj2 (surveillan* or monitor* or observat* or wait* or manag*)).tw.
6	((deferr* or delay*) adj2 (treat* or therap*)).tw.
7	4 or 5 or 6
8	3 and 7
9	randomized controlled trial.pt.
10	controlled clinical trial.pt.
11	randomi?ed.tw.
12	randomly.tw.
13	trial.tw.
14	RCT*.tw.
15	groups.tw.
16	9 or 10 or 11 or 12 or 13 or 14 or 15
17	8 and 16
18	limit 17 to english language
19	limit 18 to yr="2018 -Current"
20	conference abstract.pt.
21	19 not 20
22	remove duplicates from 21

Using a modified Cochrane sensitivity maximizing filter for identifying randomized controlled trials in Medline (https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies; accessed 28/08/2023

Appendix B: Excluded Studies

Article	*PMID/DOI/link*	*Reason for exclusion*
Enikeev 2020	https://dx.doi.org/10.1016/j.clgc.2020.05.008	Systematic review with different inclusion criteria
IP9 – ATLAS 2024	NCT06280781	No outcome of interest
Klotz 2020	https://dx.doi.org/10.1016/j.eururo.2019.10.007	No outcome of interest
Matsukawa 2024	https://doi.org/10.1016/j.euo.2023.10.010	No intervention of interest
Mineo Bianchi 2020	https://dx.doi.org/10.1016/S2666-1683(20)33632-6	Excluded publication type
PCASTT-UK 2019	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01965723/full	Excluded publication type
Schiavina 2021	https://dx.doi.org/10.1016/j.urolonc.2020.10.018	No outcome of interest
Van Blarigan 2024	https://doi.org/10.1016/j.euo.2023.10.012	No intervention of interest