DRAFT 2025 Guidelines for the Early Detection of Prostate Cancer in Australia - Pending NH&MRC approval

Main editor

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Sections

Guideline developer

The Prostate Cancer Foundation of Australia was responsible for developing these Guidelines.

Dedication

These Guidelines are dedicated to all men in Australia living with prostate cancer, and their families.

Acknowledgements

In the spirit of reconciliation, we would like to acknowledge the Traditional Custodians of Country throughout Australia and their connections to land, sea and community. We pay our respects to their Elders, past and present, and extend that respect to all Aboriginal and Torres Strait Islander Peoples today.

We acknowledge all those involved in the development of the 2025 PSA Guidelines. The revision of these Guidelines involved the commitment and contribution of many people.

Terminology

Throughout these Guidelines, we have endeavoured to use culturally appropriate, respectful and inclusive language that reflects the diverse Australian community and is accessible to all. In the development of these Guidelines, we have consulted extensively with community stakeholders to ensure the terminology used is representative of the individuals and communities the Guidelines apply to and have sought to adopt language that is clinically accurate, non-discriminatory and sensitive to all. We acknowledge that there are multiple ways people identify themselves and that language is constantly evolving. All terminology within the Guidelines is used respectfully throughout.

Gendered language

Anyone with a prostate, regardless of race and background, can be diagnosed with prostate cancer. This includes transgender women, male-assigned non-binary people or intersex people. In developing these Guidelines, the Guideline Review team considered the specific healthcare challenges and barriers to healthcare engagement experienced by men; the needs of transgender, non-binary and gender diverse communities; and principles of gender-inclusive language.

Worldwide, cancer is the second leading cause of non-communicable disease deaths in men, with prostate cancer the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men *[135]*, *[348]*. Yet men are largely absent from global and regional health-related policies *[125]*, *[124]*. There is robust evidence of what works in men's health *[124]*, *[150]*, *[192]*, *[196]*, *[248]*, *[262]*, *[337]*, including men's outcomes from cancer which can be improved through gender-targeted interventions on prevention, diagnosis, treatment, and care *[125]*. Increasingly there are calls for health policies to reflect gendered patterns in cancer care utilisation for men including approaches to practice that take account of all aspects of gender and their intersection with equity issues, such as race, class and sexuality *[125]*.

Men experience specific healthcare challenges *[267]*, as well as barriers to healthcare engagement such as beliefs about gender norms, social determinants of health and concepts of masculinities *[248]*, *[325]*, *[349]*. In addition to system, structural and cultural barriers to healthcare experienced by all people, men experience further individual barriers to care access *[248]*' *[242]*. Men are more likely to delay healthcare seeking, and access care less often, leading to reduced opportunities for education, assessment and treatment that have the potential to improve health outcomes *[242]*.

In relation to prostate cancer screening, traditional masculine ideals, hesitance about physical examination, stoicism and reluctance to discuss urological health are common barriers to men engaging with screening/testing programs *[242]*. Key to engaging men in primary health care is the therapeutic alliance, and the manner in which health professionals interact with men *[306]*. This includes using tailored communication such as language adaptations, reducing use of jargon, and avoiding negative reflections on masculinity *[306]*. A review of current English language clinical practice guidelines/optimal care pathways for prostate cancer indicated that seven out of nine guidelines use gender-specific terms (man/men) *[7]*, *[193]*, *[265]*, *[172]*, *[198]* including both current Australian guidelines *[290]* and optimal care pathways *[62]*, in alignment with these findings. As such, throughout the Guidelines the terms male/men are used.

Male/Man

'Male' refers to a person who has a male sex assigned at birth and is a biological term. 'Man' refers to an adult male, and is a gendered term that refers to a person's internal perception of masculinity *[113]*. Throughout this Guideline, where possible, we use 'male' when referring to a person with a prostate, except when referencing material in the public domain, where 'man' or 'men' may be used.

While this Guideline applies male pronouns, we acknowledge that people assigned male at birth who identify as members of the transgender and LGBTIQA+ *[112]* populations are also impacted by prostate cancer and experience unique challenges. These can include encountering heteronormative attitudes in the healthcare system, navigating the impact of changing sexual function and a homosexual identity, and poor healthcare provider understanding of the needs of sexually and gender diverse people *[177]*, *[288]*, *[327]*. There is limited evidence on the experiences and needs of transgender women in terms of early detection and management of prostate cancer *[288]*. Access to gender-sensitive care is essential to ensure healthcare meets these patients' needs. Refer to Resources for prostate cancer in sexually and gender diverse people.

Aboriginal and Torres Strait Islander males

We have consulted extensively with Aboriginal and Torres Strait Islander community members and content experts and sought guidance on the naming protocols used in the preparation of the Guidelines. We respectfully use the term 'Aboriginal and Torres Strait Islander males' throughout these Guidelines in accordance with the guidance received, acknowledging that there is a wide range of nations, cultures and languages across mainland Australia and throughout the Torres Strait and that there is no single Aboriginal or Torres Strait Islander identity.

Black males of sub-Saharan ancestry

We acknowledge that Black males of sub-Saharan ancestry are from diverse backgrounds, and may include men with ancestral links to Africa, the Caribbean or other places. In this Guideline, we respectfully use the collective phrase 'Black males of sub-Saharan ancestry' when referring to these men.

Priority populations

Priority populations are specific Australian population groups that often experience poorer health outcomes and may face barriers to accessing healthcare *[140]*, *[61]* Targeted and tailored health interventions and resources are necessary for priority populations to deliver equitable healthcare to all Australians. Considerations for priority populations in the context of prostate cancer are detailed in Section C: Priority populations.

Australian Institute of Health and Welfare. Cancer data in Australia [Internet]. Canberra: Australian Institute of Health and Welfare, 2024 [cited 2025 May. 14]. Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia

General practitioners and medical specialists

Men will engage with a number of health professionals in the course of PSA testing and subsequent management of prostate cancer including general practitioners in the primary health care setting and other health professionals providing care in specialist settings. We acknowledge that general practice is a specialty in its own right, requiring specific training and skills. We also acknowledge rural generalists with advanced skills work in both primary care and other settings. For simplicity, we differentiate 'specialists' and the 'specialist setting' as those providing secondary and tertiary care such as urologists, radiation oncologists and medical oncologists.

Review

These Guidelines were developed using a rigorous, multi-step, systematic method involving a Guideline Review team which was made up of a Project Steering Committee, two Advisory Groups, an Expert Advisory Panel, 12 Expert Advisory Panel Working Groups and an Executive Team. When referencing the collective input of the Guideline Review team we have used 'Review' as a collective term to refer to any and all processes and people involved in development of the Guidelines such as systematic reviews, Working Group discussions or other elements used to generate recommendations.

High/Higher risk

Following the approaches used in recent international prostate cancer early detection guidelines, males are considered to be at high or higher risk if they have a risk of clinically significant prostate cancer or prostate cancer death that is at least double that of the overall risk for the Australian male population.

List of abbreviations

Abbreviation	Definition
AI	Artificial intelligence
AIHW	Australian Institute of Health and Welfare
BRCA1	Breast cancer type 1 susceptibility gene
BRCA2	Breast cancer type 2 susceptibility gene
bpMRI	Biparametric magnetic resonance imaging
CALD	Culturally and linguistically diverse
CAP	Cluster Randomized Trial of PSA testing for Prostate Cancer
CI	Confidence interval
CT	Computed tomography
DRE	Digital rectal examination
EAP	Expert Advisory Panel
ERSPC	European Randomised Study of Screening for Prostate Cancer trial
HR	Hazard ratio
ISUP grade	International Society of Urological Pathology grade group system (Refer Gleason Score and ISUP Grade)
LGBTIQA+	Lesbian, gay, bisexual, transgender, intersex, queer, asexual and other sexually or gender diverse people
MBS	Medicare Benefits Schedule
MCID	Minimal clinically important difference (Refer Minimal clinically important differences)
mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
MSOAP	Medical specialist outreach assistance program
NHMRC	National Health and Medical Research Council
PCFA	Prostate Cancer Foundation of Australia
PECO	Population, exposure, comparator, outcome (research question format)
PICO	Population, intervention, comparator, outcome (research question format)
PI-RADS	Prostate Imaging-Reporting and Data System (Refer PI-RADs score)
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial
PSA	Prostate specific antigen
PSAD	Prostate specific antigen density
PSC	Project Steering Committee
PSMA PET/CT	Prostate-specific membrane antigen positron emission tomography/computed tomography
QOL	Quality of life
RCT(s)	Randomised-controlled trial(s)
RR	Relative risk
TNM	Tumour, nodes, metastasis (Refer TNM staging prostate cancer)
TRUS	Trans-rectal ultrasound

Abbreviation	Definition
5-ARIs	5-alpha reductase inhibitors
µg/L	Micrograms per liter

Preface

Prostate cancer is the most commonly diagnosed cancer in Australia and the second most common cause of cancer-related death among Australian men, claiming the lives of nearly 4,000 Australian men every year *[404]*.

In the eight years since the release of the 2016 Clinical Practice Guidelines for PSA Testing and Management of Test-Detected Prostate Cancer ('the 2016 Guidelines') an estimated 29,078 Australian men have died from prostate cancer. Over future years, projections published in The Lancet Public Health estimate that between 2020 and 2044, 600,329 Australian men will be diagnosed with prostate cancer and 116,385 men will die of prostate cancer *[4]*. In 2024, prostate cancer was one of the top 10 causes of premature death among Australian men, accounting for nearly 42,000 years of life lost.

The 2016 Guidelines, approved by Australia's National Health and Medical Research Council, set out recommendations to meet the competing challenges of reducing the burden of Australia's most prevalent cancer, while managing concerns about the potential risks of overdiagnosis and over-treatment. We acknowledge with appreciation the work of all those involved in developing the 2016 Guidelines, particularly the leadership of Professor Villis Marshall AC and Professor Bruce Armstrong AM.

Much has changed since 2016, with the evolution of medical technology, significant changes inf clinical practice, and the expansion of specialist nursing services and other supports that help to guide consumer decision making.

The literature from long-term trials of PSA testing has also matured, with evidence to demonstrate PSA testing can reduce prostate cancer mortality by approximately 30% over 22 years of follow up *[183]*.

Moreover, the introduction and widespread adoption of pre-biopsy triage with multiparametric magnetic resonance imaging (mpMRI) and increased uptake of active surveillance in Australian practice have dramatically decreased the risks of harm associated with the use of PSA alone as a testing strategy. Evidence suggests up to 84% of Australian men now undergo prebiopsy mpMRI and the proportion of men with low-risk prostate cancer opting for active surveillance has increased from 66% in 2015 to 80% in 2021 *[406]*.

In parallel, a number of consumers have expressed dissatisfaction with the 2016 Guidelines, and in particular, criticism of the absence of community education and awareness programs. These frustrations have been compounded by perceived inconsistent interpretation of the 2016 recommendations in practice, and lack of action to update the Guidelines in step with new and emerging evidence *[204]*.

Recognising the need for a new approach, in 2022 Prostate Cancer Foundation of Australia received the support of the Australian Government Department of Health, Disability and Ageing to lead an expert review of the 2016 Guidelines, with the aim to produce an evidence-based set of recommendations for uniform implementation in the Australian context.

In accordance with the National Health and Medical Research Council (NHMRC) Guidelines for Guidelines, the review was registered with the NHMRC, and a Project Steering Committee was established to oversee the review, supported by an Expert Advisory Panel and Working Groups comprised of national and international experts and consumer representatives. The exhaustive undertaking included the review of the 12 clinical questions and the corresponding 21 Patient/Population/Problem, Intervention, Comparison, and Outcome (PICO) questions from the 2016 Guidelines to inform a systematic evaluation of existing, new, and emergent evidence, nationally and internationally. The evaluation process included the input of consumers, medical and scientific experts with knowledge in each of the specific areas being considered.

We commend their work.

Equally, we place on record our appreciation to the many additional consumers, service providers, clinicians, health professionals, advocates, and community members who contributed to the review.

Importantly, in publishing these new 2025 Clinical Practice Guidelines for the Early Detection of Prostate Cancer, Australia will be among the first nations in the world to set in train a transition from an informal model of discretionary testing to a planned testing program that supports the early detection of prostate cancer on a national scale. An evidence-based approach to harm minimisation and risk assessment will be the key to success, alongside a national investment in implementation, education, evaluation, and ongoing research. Recommendations on each of these priorities have been codified in the report and aim to ensure that this body of work results in meaningful and effective outcomes. In addition, each Recommendation has a review date of no more than five years, subject to emerging evidence. Unlike the circumstance with the 2016 Guidelines, it is imperative that the draft 2025 Guidelines be kept up to date with continual monitoring of evidence and practice and reviewed within five years. Vigilance in this regard is necessary to ensure the greatest benefit to health outcomes for the Australian community.

Ultimately, this body of work reflects a shared vision and a collective effort towards zero deaths from prostate cancer, acknowledging that if we apply our knowledge to detect the disease early and treat it in a timely and effective way, we can defeat it.

Introduction

Prostate cancer is a major burden on our community and a major threat to the health of Australian men. It is the most commonly diagnosed cancer among adults, and the second-leading cause of cancer-related death among men, accounting for 16% of all cancers diagnosed and 13% of all male cancer-related deaths *[404]*.

Each year, more than 26,000 Australian men are newly diagnosed, and almost 4,000 will die of the disease. There are more than 250,000 Australian men alive today after a diagnosis, with high numbers continuing treatment, contributing to health expenditure nearing $1.5 billion each year, including around 20% of all cancer-related expenditure on the Pharmaceutical Benefits Scheme *[387]*.

With an ageing and growing population, and increasing numbers of men being diagnosed each year, the burden of prostate cancer will continue to weigh more heavily on the Australian community. The individual and public costs of treating advanced cancer are particularly high, in financial terms conservatively estimated to be around 10 times the cost of treating early-stage localised disease *[404]*.

Against this backdrop, the early detection of prostate cancer must be considered a national priority.

Background

The *Draft 2025 Clinical Practice Guidelines for the Early Detection of Prostate Cancer* ('Draft 2025 Guidelines') supersede the *2016 Clinical Practice Guidelines for PSA Testing and Management of Test-Detected Prostate Cancer* ('2016 Guidelines').

While the 2016 Guidelines accurately reflected a decade of evidence relevant to the standards of practice current at the time, the decision to revise the Guidelines took the important step of acknowledging the need to consider new and emerging research in context of advances in medical and scientific knowledge, and particularly, the way prostate cancer is diagnosed, treated, and managed.

Notably, the Draft 2025 Guidelines reflects progress in reducing the potential burden of diagnosis of low-risk prostate cancer, mitigating the risks of overtreatment and shifting the balance of benefits and harms to provide scientific support for a planned testing program in the early detection of prostate cancer.

Purpose and Scope

These Guidelines are the culmination of an exhaustive two-year-long review of the *2016 Clinical Practice Guidelines for PSA Testing and Management of Test-Detected Prostate Cancer*.

The review was commissioned by the Commonwealth Department of Health, acknowledging that an update was required to ensure alignment with the latest evidence and best practice care, establishing a robust evidence-base for updated recommendations, tailored to the Australian context, and aligned with existing and emergent optimal care pathways for prostate cancer.

In particular, the review set out to evaluate the impacts of potential new strategies for early detection of prostate cancer, including but not limited to reconsideration of:

- The absence of a clear and specific recommendation on testing for men at high risk of clinically significant prostate cancer, for example those with a strong family history of prostate cancer.
- The recommended two-yearly testing intervals for men at a high risk of prostate cancer.
- Standardising a guideline recommendation on the use of Multiparametric Magnetic Resonance Imaging (mpMRI) prior to prostate biopsy in the diagnosis of prostate cancer, following MBS listing of mpMRI scans for diagnosis and active surveillance of prostate cancer in 2018, after the original guidelines were released.
- The recommendation against testing men over the age of 70, in context of new findings that ceasing testing at age 70 may be premature and higher rates of newly diagnosed men in this age bracket have metastatic disease at point of diagnosis.
- Updating the immediate management and treatment of test-detected prostate cancers to reflect the latest standards of care.

In commissioning this review, the Commonwealth set out clear priorities, including wide-ranging consultation with a cross-section of stakeholders who comprehensively represented the experience and views of researchers, policy makers, practitioners, peak bodies, consumers, community health associations, and the general public.

As such, this document is presented in two parts. Firstly, the 2025 Guidelines. And secondly, a Dissemination Plan, which includes Implementation Priorities and Recommendations outlining necessary actions towards implementation and monitoring of this implementation. Of particular note, the Dissemination plan recommends specific strategies for priority populations, and highlights the need for ongoing evaluation and research to maintain the highest standards of diagnosis and care for Australian men.

While it was outside the scope of the review to conduct a full economic analysis of the recommendations in practice, the need for a systematic and detailed economic evaluation has been identified as an Implementation Priority. Likewise, the review did not include scope to consider any implications of an updated testing framework on the item numbers listed for specific prostate cancer related diagnostic items (e.g PSA, mpMRI) within Australia's Medicare Benefits Schedule. Instead, this has also been identified as an Implementation Priority.

In preparing these final Draft 2025 Guidelines, the Steering Committee and Expert Advisory Panel considered 11 clinical questions addressing 20 PICOs (Population, Exposure, Comparator, Outcome framework) undertaking 17 separate systematic reviews, analysing over 27,000 abstracts, and evaluating over 1,100 full-text published articles for relevance to the questions at hand. The public consultation included three rounds of engagement, resulting in more than 200 formal submissions containing 1,400 individual data points for evaluation.

The Draft 2025 Guidelines have synthesised the findings into recommendations that provide evidence-based criteria for individual risk assessment, decision support, and testing for prostate cancer using the prostate specific antigen (PSA) blood test, in addition to providing clinicians with clear guidance on the use of mpMRI prior to biopsy in the diagnostic process, as well as criteria for assessing whether a prostate biopsy is required. Specifically in relation to the management of test-detected prostate cancer, the Draft 2025 Guidelines also inform joint patient-clinician decision support on the most appropriate treatment pathways for particular grades of prostate cancer, with new clarity on recommendations for men who meet the clinical criteria for active surveillance or watchful waiting.

Strength of evidence

The Draft 2025 Guidelines have been developed based on a list of clinical questions relevant to the early detection of prostate cancer in the Australian context. Evidence-based recommendations have been presented based on the strength of evidence, evaluated according to GRADE methodology by experts in each of the relevant fields. Where relevant evidence was unavailable from systematic reviews undertaken, Consensus-based recommendations were developed. Any limitations in evidence have been acknowledged accordingly. The recommendations are supported by Good Practice Statements where it is appropriate and necessary.

Reducing risks of death

When prostate cancer is detected early, the prospects for curative treatment and long-term survival increase significantly. The Draft 2025 Guidelines therefore aim to promote the early detection of prostate cancer, mitigate the risks associated with unnecessary treatment and reduce risks of death for Australian men impacted by the disease.

Of the 26,364 Australian men expected to be diagnosed with prostate cancer in 2024, 416 (1.8%) are estimated to be under the age of 49, 3,233 (12.3%) will be aged 50 to 59, 9,559 (36.3%) will be aged 60 to 69, 9,584 (36.3%) will be 70 to 79, and 3,572 (13.6%) will be over age 80.

And while the risk of developing clinically significant prostate cancer increases with age, prostate cancer diagnosed at a younger age is more likely to cause premature death. The Draft 2025 Guidelines therefore take age into account when making recommendations for early diagnosis.

In addition to age, the Draft 2025 Guidelines also consider the available evidence on other risk factors, including genetics, family history of disease, and black sub-Saharan ancestry. In doing so, the Draft 2025 Guidelines aim to enable clinicians and health professionals to appropriately assess individual risk factors, resulting in offering testing to individuals most likely to benefit from early diagnosis while avoiding over-testing in populations less likely to benefit. This will in turn reduce the rate of diagnosis of low-risk prostate cancer, mitigate the potential for unnecessary treatment in those unlikely to benefit, and customise care to meet the individual's needs.

Importantly, the Draft 2025 Guidelines establish a clinical standard of diagnostic care for implementation across different health settings, ensuring that all Australian men can be given access to high-quality and consistent testing practices. In essence, the Draft 2025 Guidelines represent a transition from the 2016 model of discretionary testing to a planned testing program that supports the early detection of prostate cancer on a national scale, minimising risks of premature death by promoting evidence-based testing criteria, early intervention, and informed decision making.

Overdiagnosis

Overdiagnosis in the context of prostate cancer refers to the detection of a prostate cancer that would not have caused symptoms or led to death during a man's natural lifetime. While so-called ‘overdiagnosed’ cancers are real cancers, they are clinically insignificant, and concerns arise not from incorrect diagnosis, but from identifying cancers that do not require treatment.

Historically, overdiagnosis has been a critical issue when examining the potential benefits of prostate cancer screening, underscoring the need for individualised and evidence-based testing strategies that can detect clinically significant cancers early, while minimising harm from unnecessary interventions. Understanding and mitigating risks of overdiagnosis are essential to preserving quality of life and help to uphold optimal care, both in terms of patient outcomes and health system efficiencies.

During the first decade of PSA testing in the United States, beginning around 1988, prostate cancer overdiagnosis in asymptomatic men was estimated to range between 29% to 44%, depending on the population studied and the testing strategies employed *[405]*. In Australia, PSA testing was introduced in the early 1990s, with an estimated rate of overdiagnosis of around 41% by 2012 *[266]*. Evidence suggests that overdiagnosis is more prevalent in settings where PSA testing is offered opportunistically, and is particularly evident among older men, while populations with access to organised testing programs experience lower rates of overdiagnosis *[407]*.

The primary cause for concern in cases of overdiagnosis is overtreatment, including surgery or radiation therapy, which can lead to life-altering side effects for no benefit in overall survival or health-related quality of life. At the health system level, overdiagnosis can make it harder to identify and manage incidence and mortality trends, increasing health care costs associated with unnecessary diagnostic testing, treatments, and monitoring.

In recognising and responding to concerns about overdiagnosis and treatment, standards of care have evolved and adapted to prevent overtreatment of indolent prostate cancers, while recognising the importance of early detection and monitoring of low-risk disease. In Australia today, over 80% of men with low-risk prostate cancers undergo active surveillance *[392]*, and the advent of new screening tools and knowledge, such as mpMRI and genomic profiling, has helped to differentiate aggressive cancers from indolent ones, helping to avoid the harms of overtreatment.

In this context, overdiagnosis is largely a thing of the past.

Harm minimisation

The 2025 Guidelines recommend risk-based testing strategies that minimise potential harms in the early detection of prostate cancer, drawing on new evidence and technologies with the objective to promote overall survival and health-related quality of life among those impacted by the disease.

Much has changed since the release of the 2016 Guidelines for PSA Testing, with significant developments in knowledge and clinical practice to promote harm minimisation. These advances have substantially reduced the risks and potential harms of early detection through:

- Risk-adapted assessment and early detection;
- the use of pre-biopsy multiparametric MRI (mpMRI);
- the widespread adoption of transperineal biopsy replacing transrectal biopsy;
- treatment of low-risk disease with active surveillance;
- increased use of focal therapy; and
- improved prevention and management of treatment-related morbidities.

Moreover, long-term observations of randomised controlled trials and modelling have found that the benefits of PSA screening are comparable to those for organised breast and bowel cancer screening programs *[416][417]*.

Risk-adapted assessment is a key concept in the early detection of prostate cancer, whereby individualised testing recommendations prevent unnecessary PSA testing among men who are unlikely to benefit from it, thereby strengthening the efficacy of testing protocols, reducing risks of mortality, and promoting harm minimisation.

Ultimately, the objective of harm minimisation remains unchanged over time, that is, to reduce a man's risks of death, while preserving optimal quality of life. In the Australian context, under the 2016 Guidelines, increasing numbers and rates of men have been newly diagnosed with more advanced prostate cancers, with significant impacts on individuals and the Australian healthcare system. Estimates suggest the cost of treating advanced and metastatic prostate cancer is around 10-times the cost of treating localised disease. According to Australian Institute of Health and Welfare data, prostate cancer accounts for around 16% of all cancer-related expenditure on Australia's Pharmaceutical Benefits Scheme and for more than 12% of all cancer-related expenditure in the Australian Health System (2020-21) *[387]*. Prostate cancer also accounts for the largest proportion of tumour-specific cancer-related expenditure in the Australian Health System, with overall expenditure of $1.8 billion per year.

Current evidence suggests that PSA testing is associated with a relative reduction of approximately 30% in the number of men who will be newly diagnosed with metastatic prostate cancer *[159]*. This finding makes it clear that by focusing on those at high risk of the disease, harnessing new evidence and diagnostic methods to promote early detection can save many lives.

Multiparametric Magnetic Resonance Imaging (mpMRI) in the Early Detection of Prostate Cancer

Among the major developments in standards of care since the release of the 2016 Guidelines for PSA Testing is the use of mpMRI prior to biopsy, reducing numbers of avoidable biopsies that had historically led to the overdiagnosis of indolent prostate cancers unlikely to cause a man harm in his lifetime. Today, prostate mpMRI to guide the selection of patients indicated for biopsy and assist in targeting lesions most likely to harbour clinically significant prostate cancer has become a practice standard in the Australian context. Evidence-based recommendations for use of mpMRI (incorporating assessment of PSA density) to triage men for biopsy, and use of mpMRI to guide targeted prostate biopsies are new and important inclusions in the 2025 Draft Guidelines.

Transperineal biopsy

Increasing uptake of transperineal biopsy has also marked a key change in the diagnosis of prostate cancer in Australia over recent years, reducing the risks of post biopsy infections and sepsis associated with transrectal procedures. Between 2022 and 2025, transperineal biopsies were conducted at over nine times the rate of transrectal biopsies (21,176 vs 2,360), accounting for 97% of rebated procedures under Australia's Medicare Benefits Schedule, representing one of the highest rates of transperineal biopsy in any jurisdiction in the world. The Draft 2025 Guidelines support the use of transperineal biopsy in the early detection of prostate cancer, recognising that the approach is today codified as standard of care within international guidelines.

Focal Therapy

A review of the role of focal therapy was outside the scope of these guidelines. However, multiple systematic reviews and prospective studies report that focal therapy—using techniques such as high-intensity focused ultrasound, cryotherapy, photodynamic therapy, and irreversible electroporation—is associated with lower rates of urinary incontinence and erectile dysfunction, with most series reporting pad-free continence rates of 94–100% and preservation of erectile function sufficient for intercourse in 47–86% of patients *[400]*.

Direct comparative studies show that focal ablation is the most significant factor associated with better recovery of sexual potency and urinary continence at both three and 12-months post-treatment, after adjusting for baseline differences *[401]*.

The literature also emphasises, however, that comparisons to other forms of treatment and the evaluation of long-term outcomes are limited, and patient selection is therefore critical. It must also be noted that urological societies worldwide are yet to endorse focal therapy as standard of care while these evidence gaps remain unaddressed. For these reasons, the 2025 Guidelines suggest that focal therapy be considered for future inclusion in view of ongoing research and emerging evidence, particularly in relation to harm-minimisation.

Rates of treatment-related morbidity

In establishing the evidence base for a structured PSA testing framework, the Draft 2025 Guidelines give due consideration to rates of treatment-related morbidities.

Urinary and erectile problems are the two most commonly reported quality of life risks of radical treatment in patients with localised prostate cancer. In a large registry-based cohort of Australian and New Zealand patients 8-12% of respondents treated with radiation or surgery reported that urinary function was a problem and 34-45% reported sexual function was a problem *[263]*.

Contemporary studies show that the use of intensity-modulated radiation therapy (IMRT) with image guidance has reduced bowel toxicity compared to older three-dimensional conformal radiation approaches *[408]*.

Robotic-assisted radical prostatectomy has largely replaced open surgery and is associated with improved short-term urinary and sexual function outcomes, although long-term declines in sexual function and urinary continence remain significant, especially after prostatectomy *[247]*.

Just as the rate of diagnosis and treatment of low-risk and low-intermediate risk prostate cancer has decreased, so has the cumulative impact of treatment-related morbidity in the Australian context. Logically, we can expect that as the number and rate of men being newly diagnosed with metastatic prostate cancer decreases, so too will rates of treatment-related morbidity associated with the management of metastatic prostate cancer.

This will be an important outcome arising from the implementation of the Draft 2025 Guidelines.

Active surveillance

The increased use of active surveillance as the initial management approach for patients with low-risk prostate cancer has enabled the decoupling of diagnosis and treatment. This mitigates many of the past problems associated with unnecessary diagnosis of low-risk disease. Active surveillance, when managed effectively, is likely to reduce the number of men at risk of the long-term side effects of definitive treatments *[409]*.

Active surveillance is currently the recommended management strategy for men with low-risk disease who are eligible for local treatment, and is now well accepted as the first line of treatment for low-risk disease in Australia and New Zealand. In 2021, 80% of patients diagnosed with low-risk localised disease were managed with active surveillance, having increased from 66% in 2015 *[392]*. Comparatively, only 3-4% of Australian and New Zealand men diagnosed with low-risk prostate cancer had a radical prostatectomy.

Watchful Waiting

Watchful waiting is a conservative strategy for managing prostate cancer that does not require immediate treatment or for which the man declines intervention. Watchful waiting in patients with significant comorbidities and those with metastatic prostate cancer reduces harm by avoiding treatment-related morbidity.

Updating these Guidelines

Medical research and clinical practice are continually evolving, and new evidence is continually emerging. Each recommendation in these Draft 2025 Guidelines has a review date of no longer than five years, subject to emerging evidence. The Guidelines should be reviewed in total, within five years of publication. Additionally, it is strongly recommended that systems be put in place for the ongoing monitoring and evaluation of emerging evidence as it arises, along with processes to update recommendations, to ensure the greatest benefit to the Australian community through timely translation of evidence to practice.

Summary

In summary, with a key focus on harm minimisation the 2025 Guidelines have drawn on the very latest evidence and practice to recommend risk-adapted strategies for maximising the benefits and minimising the harms of PSA testing in men who may be at risk of prostate cancer, but without symptoms suggestive of prostate cancer. For men at an average risk of prostate cancer, the Draft 2025 Guidelines provide clear and consistent recommendations that aim to promote early detection, while preventing harm. The basis on which these Guidelines have been developed reflects a depth of knowledge and experience that has been collected over decades and reconsidered in the context of new and emerging evidence and standards of care, with clear potential to ensure early detection of clinically significant disease, preserve men's quality of life, and improve overall survival outcomes.

Plain English summary

Who are these Guidelines for?

These Guidelines have been developed to support clinicians in the early detection and management of prostate cancer for Australian males. Although they have been written for general practitioners (GPs), urologists and other health professionals, in this section they are explained for people who don't have a medical background.

What is prostate cancer?

Prostate cancer occurs when abnormal cells develop and grow in the prostate. These abnormal cells can continue to multiply in an uncontrolled way. They sometimes spread outside the prostate into nearby or distant parts of the body. If the cancer is small, stays inside the prostate gland and grows slowly, it may never cause a problem. In some males, the cancer may grow more quickly and can spread outside the prostate to other parts of the body.

Who gets prostate cancer?

Anyone with a prostate, regardless of race and background, can be diagnosed with prostate cancer. This includes transgender women, male-assigned non-binary people or intersex people.

Prostate cancer is the most commonly diagnosed cancer in Australia. In 2024, more than 26,000 Australian males were diagnosed with prostate cancer and almost 4,000 males died from the disease. Nearly 72 Australian males are diagnosed every day, with 1 in 5 males at risk of being diagnosed in their lifetime. This is because the risk of developing prostate cancer increases as you get older.

Apart from age, there are several other factors that increase your risk of developing prostate cancer including:

- A family history of prostate cancer - if your father, brother or other male family members have been diagnosed with prostate cancer
- Being a Black male with sub-Saharan African ancestry
- Having gene mutations like BRCA2, or someone with breast cancer or ovarian cancer, or Lynch Syndrome in your family.

How is prostate cancer detected?

The first step in detecting prostate cancer is a simple blood test that measures the level of a protein called prostate-specific antigen (PSA) in your blood. If your PSA levels are high for your circumstance, it might call for further investigation. Your doctor may recommend further tests to see what is causing the high levels of PSA. In some cases cancer may be found, but a higher than expected PSA level does not always mean you have cancer, so further testing will be required to rule out or diagnose prostate cancer.

Why is early detection important?

Early detection and management of prostate cancer can be lifesaving. In the early stages of prostate cancer there may be no symptoms, so testing for prostate cancer may detect a potentially harmful cancer before it spreads, improve the chances of treatment being successful, and reduce your risk of dying from prostate cancer.

Most prostate cancers are slow growing, so if they are detected early enough there is an excellent chance of survival. In Australia, over 98% of men with early-stage prostate cancer will be alive 5 years after diagnosis. Unfortunately, only 36% of prostate cancers are detected in the early stage (stage 1 of the disease), when prostate cancer can be most effectively treated. For men who are diagnosed late, only 36% will be alive 5 years after diagnosis.

When should I start testing for prostate cancer?

These Guidelines recommend testing for prostate cancer from the age of 50 for most males.

If you are at higher risk of prostate cancer, e.g., you have a family history of prostate cancer, you are a Black male with Sub-Saharan African ancestry, or you have certain genetic mutations, the Guidelines recommend testing for prostate cancer from the age of 40.

From age 40, if you are interested in your prostate health, you can talk to your GP about starting testing, even you do not have a family history.

There are a number of evidence-based resources available to help you decide when, or if, to start testing for prostate cancer. Contact the Prostate Cancer Foundation of Australia (PCFA) for more information on the details below.

Where can I find out more about prostate cancer and being tested for prostate cancer?

General practitioner (GP)

You can talk to your GP about prostate cancer, your risk of developing prostate cancer and about being tested for prostate cancer. You can ask your GP to order a PSA test for you and your GP can refer you for further testing if needed.

Resources for the LGBTIQA+ populations

Dedicated information for transgender women, male-assigned non-binary people or intersex people can be found here:

- Prostate Cancer Foundation of Australia: Understanding Prostate cancer for LGBTIQA+ people
- Cancer Council: LGBTQI+ People and Cancer: A guide for people with cancer, their families and friends

Prostate Cancer Foundation of Australia

The Prostate Cancer Foundation of Australia (PCFA) have developed a range of evidence-based resources about prostate cancer, PSA testing, information for newly diagnosed men and information on specific treatments for prostate cancer.

These resources can be accessed:

- As **printed booklets**: to order. fill in and submit the order form, or call 1800 22 00 99 or email enquiries@pcfa.org.au
- As **downloadable PDF files** available from this link
- Via the **Prostate Cancer Toolkit website**: https://www.prostate.org.au/

If you would like to **speak to someone** about prostate cancer, including being tested for prostate cancer, you can call the Prostate Cancer Specialist Telenursing Service on **1800 22 00 99**. When you call, you will be connected to a Prostate Cancer Specialist Nurse who can:

- Provide easy to understand evidence-based information and resources about all aspects of prostate cancer
- Provide you with support to make decisions about being testing for prostate cancer
- Help you to understand PSA testing, what a prostate cancer diagnosis means, treatment options and ways you can manage treatment side effects
- Offer relevant practical and emotional support tailored to your needs
- Link you with local support networks including Prostate Cancer Support Groups and locally based Prostate Cancer Specialist Nurses

You can also **email** the Prostate Cancer Specialist Telenursing Service: telenurse@pcfa.org.au or fill out an **online enquiry form**: https://www.pcfa.org.au/telenursing-request-form/

For any other information, questions or enquires about prostate cancer, visit the PCFA website: https://www.pcfa.org.au/

Executive Summary

About this guideline

The 2025 Guidelines provide evidence-based recommendations and strategies for individualised risk assessment and harm minimisation, for the early detection of prostate cancer.

The risks and potential harms of PSA testing have markedly changed since the release of the 2016 Guidelines for PSA testing.1 These potential harms included:

- diagnosis of clinically insignificant prostate cancer
- anxiety and stress caused by a positive test
- risks associated with transrectal prostate biopsies in particular infection and sepsis
- overtreatment of clinically insignificant prostate cancer
- treatment related morbidity including urinary incontinence erectile dysfunction and bowel problems.

Since 2016, advances in diagnostic technologies, in parallel with the evolution of clinical practice, have substantially reduced the risks and potential harms of PSA testing in Australia through:

- risk adapted assessment and early detection
- the use of pre-biopsy multiparametric MRI (mpMRI)
- the widespread adoption of transperineal biopsy replacing transrectal biopsy
- increased uptake of active surveillance as the first line of treatment for low-risk disease uncoupling diagnosis and treatment
- increased use of focal therapy
- improved management and prevention of treatment related morbidity.

In addition, longer term results from the randomised trials of PSA screening have shown relative risks and numbers needed to invite to screening to be comparable to the relative risks and numbers needed to screen for the organised screening programs of breast and bowel cancer *[183]*, *[382]*, *[383]*, *[384]*.

Methods and processes used to develop the Guidelines

Project governance

For information about the Review governance structure and member organisations refer to Appendix 1: Governance structure and group membership.

Conflicts of interest

For interest declarations and conflict of interest management refer to the Administrative Report.

Previous version of the Guidelines

These Guidelines are the result of the review and update of 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'). These Guidelines can be accessed via the PCFA website: 2016 Guidelines.

Developing the recommendations

These Guidelines have been developed by following the NHMRC Guidelines Handbook National Health and Medical Research Council *[2]* and Grading of Recommendations, Assessment, Development and the Evaluation (GRADE) evidence to decision processes [302] so as to align with with the 2016 NHMRC Standards for Guidelines [256]. More details on the development of these Guidelines can be found in the Technical Report.

The GRADE evidence to decision framework was used to develop the recommendations and determine the strength of recommendations by assessing the following factors:

- 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 the 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.

All stages in the process to develop these Guidelines involved the Expert Advisory Panel and subject-specific Working Groups which brought together multidisciplinary health professional expertise and consumer perspectives. More information can be found in Appendix 1: Governance structure and group membership.

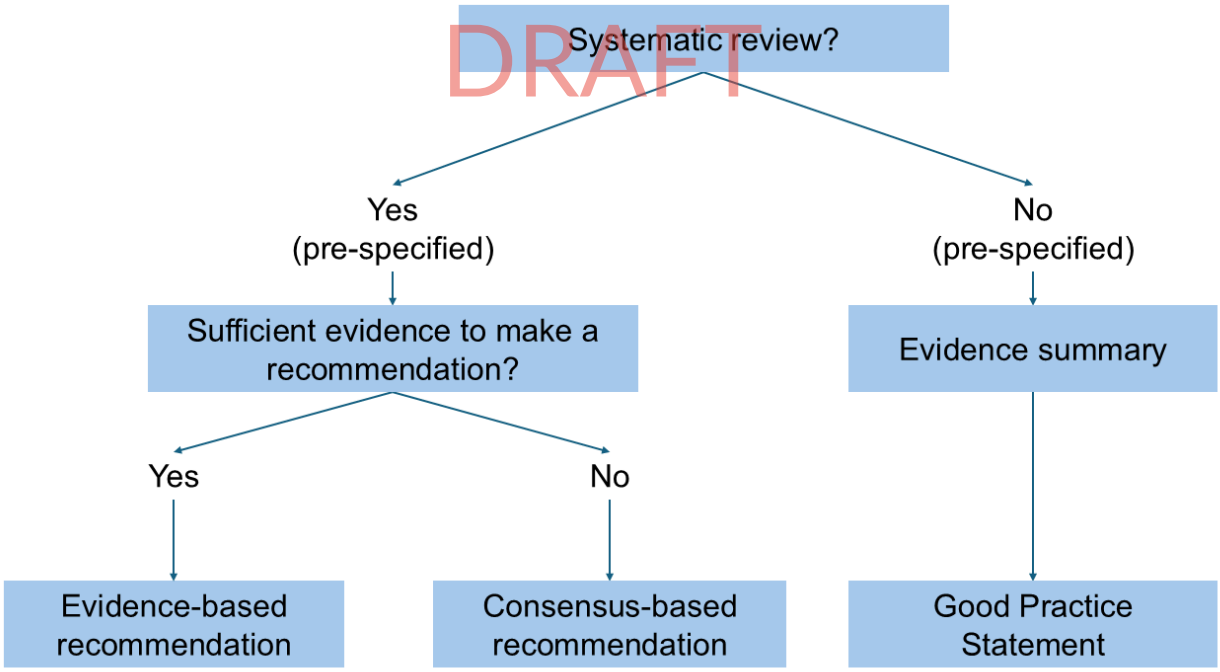
Clinical questions were developed by the Working Groups and Expert Advisory Panel following review of the 2016 Guidelines, consideration of advances in technology and current clinical care for the early detection of prostate cancer. To address each clinical question the technical team and Working Groups developed one or more questions structured according to the populations, interventions, comparisons, outcomes of interest (PICO) or populations, exposures, comparisons, outcomes of interest (PECO) (refer Appendix 2: Clinical questions and PICOS/PECOS). Each PICO or PECO question was addressed by a systematic review (refer Technical Report). 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.

Types of recommendations

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 review.
- 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.



More information can be found in the Technical Report.

Strength of evidence-based recommendations

GRADE uses two categories for the strength of evidence-based recommendations:

- **Strong recommendations**; or
- **Conditional recommendations.**

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

Recommendation strength	Criteria
Strong recommendation 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 recommendation 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	**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

Harms may outweigh benefits for the majority, but not for everyone. The majority of patients would likely not want this option.	• 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.

More information can be found in the Technical Report.

DRAFT Clinical Practice Recommendations for the 2025 Guidelines for the Early Detection of Prostate Cancer in Australia

The DRAFT clinical practice recommendations for the 2025 Guidelines for the Early Detection of Prostate Cancer in Australia and supporting information can be found in Sections A to G.

All recommendations will be reviewed within five years, subject to emerging evidence

A PDF of the summary of the recommendations can be downloaded using this link summary of recommendations.

Target setting

These DRAFT Guidelines are intended for health professionals in primary care and specialist urological settings, working with asymptomatic men who are considering, or eligible for, prostate specific antigen (PSA) testing. The recommendations in these DRAFT Guidelines are intended for people with training in medicine or other health sciences. They are not intended for the general public.

What has changed

Much has changed since 2016.

The literature from long term PSA testing trials has matured demonstrating improved prostate cancer metastasis free and overall survival from early detection. In addition, the introduction and widespread adoption of pre-biopsy triage with mpMRI and the increased utilisation of active surveillance in Australian practice have dramatically decreased the previously reported harms associated with the use of PSA alone as a testing strategy.

The 2025 Guidelines extend the work initiated in 2016, shifting the focus in two significant aspects:

1. **Firstly,** the transition from an discretionary testing program to a planned testing program; and
2. **Secondly,** the transition from a focus on PSA testing to a focus on the early detection of prostate cancer.

This paradigm shift is supported by evidence-based strategies for risk assessment and harm minimisation while ensuring the necessary emphasis on contemporary understanding of the importance of decision support, consumer preferences, masculinity and men centred care.

The 2025 Guidelines have evolved in a number of ways. A summary of Guideline changes from 2016 to 2025 is presented in Table 1 below.

Table 1: Summary of changes, 2016 Guidelines to draft 2025 Guidelines

2016 Guidelines	2025 draft Guidelines
1. Risk	
Risk quantified (average, x times higher than average).	Risk simplified to 'males at higher risk', i.e., a risk of clinically significant prostate cancer or prostate cancer death that is at least double that of the overall risk for the Australian male population.
No recommendations based on risk.	Seven recommendations related to risk with the following populations considered to be at higher risk of clinically significant prostate cancer: • Males with a significant* family history of prostate cancer • Black males of sub-Saharan ancestry • Males with a *BRCA2* gene mutation * Significant family history: a brother diagnosed with prostate cancer, their father diagnosed with prostate cancer before the age of 65, or two or more second degree relatives who died of prostate cancer. Refer Section A: Risk assessment
No recommendations based on family history of prostate cancer.	**1.1.1 Strong recommendation** We recommend that males are considered as being at higher risk of prostate cancer mortality for the purposes of PSA testing in the primary care setting if they have significant family history: • A brother diagnosed with prostate cancer • A father diagnosed with prostate cancer before the age of 65 • Two or more second degree relatives who died of prostate cancer. In this population the risk of dying from prostate cancer is at least double that of non-higher risk males.
2. Decision support	
2016 Guidelines	**2025 draft Guidelines**
Part of PSA Testing Strategies.	As decision support underpins all aspects of a planned testing program for the early detection of prostate cancer, Decision Support is a standalone section. Refer Section B: Decision support
Offer evidence-based decisional support to men considering whether or not to have a PSA test, including the opportunity to discuss the benefits and harms of PSA testing before making the decision.	In accordance with current best practice, approaches to decision support should take into account personal preferences and circumstances. Decision support is more likely to be required in circumstances where there are alternative management options. Decision support approaches can include: • Informal discussions phrased in terms of options and potentially a recommendation

2016 Guidelines	2025 draft Guidelines
	• In-depth discussions explaining benefits, risks and timelines of testing • Provision of general written information, and/or provision of decision support tools • Referral to digital resources such as websites or apps from reputable organisations. Refer Section B: Decision support
3. Priority populations	
2016 Guidelines	**2025 draft Guidelines**
Not identified in Recommendations.	Aboriginal and Torres Strait Islander males are considered a priority population, recognising their lower survival compared with non-Aboriginal and Torres Strait Island men. Refer Aboriginal and Torres Strait Islander males
4. Digital rectal examination (DRE)	
2016 Guidelines	**2025 draft Guidelines**
DRE in the primary care setting is not recommended as a routine addition to PSA testing and risk assessment.	No change. Refer 4. Digital rectal examination
5. Primary health care setting - PSA testing	
2016 Guidelines	**2025 draft Guidelines**
Nil Strong recommendations	**Two Strong recommendations** **5.3 Strong recommendation** We recommend offering males aged 50 to 69 years PSA testing every two years. If total PSA is 3.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, offer referral for further investigation. Refer 5.1 and 5.2 Good practice statements. **5.4 Strong recommendation** We recommend offering PSA testing to males who are at higher risk* Refer 5.5 Consensus recommendation for testing regimen. * Males are considered to be at higher risk if they have a risk of clinically significant prostate cancer or prostate cancer death that is at least double that of the overall risk for the Australian male population. Higher risk includes, but is not restricted to, males with certain patterns of family history, Black males of sub-Saharan African ancestry and/or males with confirmed BRCA2 gene mutations. Refer Section A: Risk assessment

2016 Guidelines	2025 draft Guidelines
Age 50 to 69 years For men not at higher risk of prostate cancer who have been informed of the benefits and harms of testing and who decide to undergo regular testing for prostate cancer, offer PSA testing every 2 years from age 50 to age 69, and offer further investigation if total PSA is greater than 3.0 ng/mL.	**Age 50 to 69 years** For males aged 50 years and over, **initiate a discussion regarding the benefits and possible harms of testing** for the early detection of prostate cancer. See 5.3 Strong recommendation above Refer Primary health care setting - PSA testing
Age under 50 years For men younger than 50 years who are concerned about their risk for prostate cancer, have been informed of the benefits and harms of testing, and who wish to undergo regular testing for prostate cancer, offer testing every 2 years from age 45 to age 69 years. • If initial PSA is at or below the 75th percentile for age, advise no further testing until age 50. • If initial PSA is above the 75th percentile for age, but at or below the 95th percentile for age, reconfirm the offer of testing every 2 years. • If a PSA test result before age 50 years is greater than the 95th percentile for age, offer further investigation. Offer testing from age 50 years according to the protocol for all other men who are not at higher risk of prostate cancer.	**Age under 50 years** We propose offering males who are not at a higher risk and who are interested in their prostate health an initial PSA test from age 40 years. • In males aged 40 to 49 years, if total PSA is 1.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation. • If total PSA is less than 1.0 µg/L, no further PSA testing is recommended until age 50 years. Refer Primary health care setting - PSA testing
Age 70 years and over Advise men 70 years or older who have been informed of the benefits and harms of testing and who wish to start or continue regular testing that the harms of PSA testing may be greater than the benefits of testing in men of their age.	**Age 70 years and over** We propose offering males aged 70 years and over a PSA test every two years subject to clinical assessment, which may include consideration of life expectancy, comorbidities, and patient values and preferences. If total PSA is 5.5 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation. We propose for males aged 70 years or over, if their PSA is less than 5.5 µg/L, continued testing be subject to clinical assessment. Refer 5. Primary health care setting - PSA testing
Males at higher risk For men whose risk of prostate cancer is estimated to be at least 2.5–3 times higher than average due to the presence of risk factors (e.g. a brother diagnosed with prostate cancer, particularly if younger than 60 years at diagnosis), and who decide to undergo testing after being informed of the benefits and harms, offer testing every 2 years from age 45–69 years. For men whose risk of prostate cancer is estimated to be at least 9–10 times higher than average due to the presence of risk factors (e.g. father and two brothers diagnosed with prostate cancer), and who decide to undergo testing after being informed of the benefits and harms, offer testing every 2 years from age 40–69 years. • If initial PSA is at or below the 75th percentile for age, advise no further testing until age 50.	**Males at higher risk** A Strong recommendation to offer PSA testing to males who are at higher risk. **See 5.4 Strong recommendation above** Refer 5. Primary health care setting - PSA testing In view of 5.4 above, we propose offering males who are at higher risk PSA testing every two years from age 40 years. • For males aged 40 to 49 years if total PSA is 1.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation. • For males aged 50 to 69 years if total PSA is 2.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation. Refer Section A: Risk assessment.

2016 Guidelines	2025 draft Guidelines
• If initial PSA is above the 75th percentile for age, but at or below the 95th percentile for age, reconfirm the offer of testing every 2 years. • If a PSA test result before age 50 years is greater than 95th percentile for age, offer further investigation.	
Aboriginal and Torres Strait Islander males Nil testing criteria.	**Aboriginal and Torres Strait Islander males** Aboriginal and Torres Strait Islander males are considered a Priority Population, however, PSA testing recommendations for Aboriginal and Torres Strait Islander males are the same as for the general population. Refer 3.1 Aboriginal and Torres Strait Islander males Refer 5. Primary health care setting - PSA testing
Life expectancy Since any mortality benefit from early diagnosis of prostate cancer due to PSA testing is not seen within less than 6–7 years from testing, PSA testing is not recommended for men who are unlikely to live another 7 years.	**Life expectancy** We suggest offering PSA testing only to males whose life expectancy is greater than seven years. Refer 5. Primary health care setting - PSA testing

6. Specialist setting - Multiparametric magnetic resonance imaging (mpMRI)

2016 Guidelines	2025 draft Guidelines
Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound-guided biopsy to determine whether another biopsy is needed.	mpMRI is now the preferred first diagnostic test following raised PSA to determine if biopsy is required. Refer 6. Specialist setting - Multiparametric magnetic resonance imaging

7. Biopsy

2016 Guidelines	2025 draft Guidelines
Take 21–24 cores in initial biopsies for the diagnosis of prostate cancer. In addition to the sextant biopsies, direct 15–18 additional biopsies to the peripheral zones of the prostate.	Biopsy is no longer considered the primary testing approach following an elevated PSA test result. • mpMRI-targeted biopsies plus systematic biopsies are recommended. • The optimal number of cores for targeted biopsy should be at least 3-4. Refer 7. Specialist setting - Prostate biopsy
Transrectal and transperineal biopsy approaches are both acceptable with respect to rates of cancer detection.	When performing prostate biopsy for the early detection of prostate cancer, an ultrasound-guided transperineal approach is preferred as there is less risk of post biopsy infection. The ultrasound images are in the axial plane as are the MRI images which facilitates more accurate target biopsies.

8. Active surveillance

2016 Guidelines	2025 draft Guidelines

2016 Guidelines	2025 draft Guidelines
CRITERIA Offer active surveillance to men with prostate cancer if all the following criteria are met: • PSA ≤ 20 ng/mL • Clinical stage T1–2 • Gleason score 6. Consider offering active surveillance to men with prostate cancer if all the following criteria are met: • PSA ≤ 10.0 ng/mL • Clinical stage T1–2a • Gleason score ≤ (3 + 4 = 7) and pattern 4 component < 10% after pathological review.	**CRITERIA** – refer 8.1 Criteria for choosing active surveillance Active surveillance should be offered to patients with low risk prostate cancer, and may be offered to patients with low to intermediate prostate cancer as below. In patients diagnosed with prostate cancer, if all the following criteria are met*: • PSA<10 µg/L • Clinical stage T1-T2a • MRI PI-RADS 3 or less • PSAD 0.15 µg/L/mL or less. Then, • Offer active surveillance to patients with ISUP Grade Group 1 • Consider offering active surveillance to patients with ISUP Grade Group 2 with less than or equal to 10% of Gleason pattern 4. *Note that in selected cases, subject to a patient's individual circumstances, active surveillance may still be offered if PSA is >10 µg/L, or clinical stage is T2b or T2c, or mpMRI PI-RADS >3, or PSAD >0.15 µg/L/mL.
Consider offering definitive treatment for: • Men with clinical stage T2b-c prostate cancer • Men with biopsy-diagnosed prostate cancer with PSA • 10.0–20.0 ng/mL who do not meet the other criteria for active surveillance • Men aged less than 60 years with either of the following: • Clinical stage T2b-c prostate cancer • PSA 10.0–20.0 ng/mL and biopsy-diagnosed prostate cancer which does not meet the other criteria for active surveillance. If the man strongly prefers active surveillance, offer repeat biopsy to ensure that disease classification is accurate.	During active surveillance, offer definitive treatment if: • Pathological progression is detected on biopsy • Patient preference. Note: Progression on mpMRI is not an indication for definitive treatment but will likely prompt the need for repeat biopsies. When considering active surveillance, take into account other factors that may be associated with the risk of future pathological progression such as total cancer length or percentage core involvement at biopsy and tumour volume. Active surveillance is not advised in patients with: • Variant histology, including sarcomatoid, small cell, cribriform • Histologic features, including intraduct, extra-prostatic extinction, lymphovascular invasion and perineural invasion.
MONITORING PROTOCOLS For men with prostate cancer managed by an active surveillance protocol, offer monitoring with PSA measurements every 3 months, and a physical examination, including digital rectal examination, every 6 months. Offer a reclassification repeat prostate biopsy within 6–12 months of starting an active surveillance protocol. Offer repeat biopsies every 2–3 years, or earlier as needed to investigate suspected disease progression: offer repeat biopsy and/or multiparametric MRI (in specialised centres) if PSA doubling time is less than 2–3 years or clinical progression is detected on digital rectal examination.	**MONITORING PROTOCOLS** – refer 8.2 Monitoring protocols for active surveillance For patients with prostate cancer who are being managed by active surveillance offer: • Initial three to six-monthly PSA measurements • Digital rectal examination periodically • Repeat mpMRI may be offered after 12 to 24 months and again at three years, or earlier, if clinically indicated • Repeat the prostate biopsy in the first 12 months at clinician's discretion e.g., where there is uncertainty regarding initial diagnostic biopsy, changes in PSA, DRE or mpMRI • Subsequent repeat prostate biopsies are usually not required in less than three years unless there are

2016 Guidelines	2025 draft Guidelines
	changes in PSA, DRE or mpMRI.
9. Watchful waiting	
2016 Guidelines	**2025 draft Guidelines**
Offer watchful waiting to men diagnosed with potentially curable prostate cancer who: • For reasons other than prostate cancer, are unlikely to live for more than another 7 years • Choose not to accept potentially curative therapy when it is offered to them.	Although included in the 2016 Guidelines, the Review determined watchful waiting is not a primary management strategy in the context of a planned testing program for early detection of prostate cancer. Watchful waiting does, however, play a secondary role in harm minimisation (versus active surveillance) in that it decreases and at times, avoids overtreatment and associated treatment morbidities. The practice of watchful waiting is a patient-centred conservative strategy for managing prostate cancer when cure is not the goal. The aim is to maximise the patient's quality of life in alignment with their initial and evolving stated goals of care. Refer 9. Watchful waiting
10. Guideline implementation and monitoring	
2016 Guidelines	**2025 draft Guidelines**
Not addressed.	Sustained and ongoing investment to support the national dissemination, implementation, monitoring and evaluation of the 2025 Guidelines for the Early Detection of Prostate Cancer in Australia, including: • Development of a national Guideline implementation and dissemination strategy to be led by Prostate Cancer Foundation of Australia with a focus on ensuring the 2025 Guidelines and associated resources are readily accessible and free of charge to all users. • Development and implementation of a national Guideline awareness and education campaign on prostate cancer risks and surveillance options for health professionals, consumers and the general public. • Development of a consumer companion to the 2025 Guidelines including: • Tailored resources for priority populations including Aboriginal and Torres Strait Islander males, LGBTIQA+, and CALD populations. • The translation of consumer resources related to the 2025 Guidelines into other languages. • An approach to ensure the ongoing monitoring, evaluation and updating of the Guidelines, for the timely identification and incorporation of new evidence as it emerges including commensurate funding and support from the Commonwealth Government. • Full health economic evaluation of the risk adapted, a planned testing program for the early detection of prostate cancer in Australia. • Support for clinical cancer outcomes registries to collect data on the outcomes of the early prostate cancer detection program, e.g., safety, harm minimisation, rates of active surveillance and quality of life parameters.

2016 Guidelines	2025 draft Guidelines
	• Alignment of approved Guidelines with Medicare Benefits Schedule (MBS), and, where MBS items do not currently apply, actions to ensure transition of these individual medical services into the MBS. Refer Section F: Guideline implementation and monitoring

Section A: Risk assessment

This section is restricted to a discussion of the individual's risk of clinically significant prostate cancer or prostate cancer specific mortality. It is beyond the scope of this review to include discussion of people's perceptions and responses to their risk of testing, diagnosis and treatment. A male's risk of developing clinically significant prostate cancer depends on multiple factors, known and unknown, resulting in a continuum of risk at any point in time and age. It is not possible to undertake such a precise risk assessment in these Guidelines. The development of tools to assess the multiple factors that determine the risk of being diagnosed with clinically significant prostate cancer, or the risk of prostate cancer mortality in each individual, is beyond the scope of this review.

Risk factors that have been interrogated for this review are:

- Age
- Family history of prostate cancer
- Black sub-Saharan African ancestry.

Further, based on the evidence considered for EAU guidelines 2025 such as that provided by Nyberg et al 2020 *[355]* it is accepted that those with a BRCA2 mutation have over double the risk of prostate cancer mortality when compared to the general population.

The risk of developing clinically significant prostate cancer increases with age. However, prostate cancer, when diagnosed at a younger age, is more likely to cause premature death. Throughout these Guidelines, age is taken into account when deciding which testing protocols to offer.

In keeping with the approaches used in recent international prostate cancer guidelines, for the purposes of this review, males are considered to be at higher risk if they have a risk of clinically significant prostate cancer or prostate cancer death that is at least double that of the overall risk for the Australian male population.

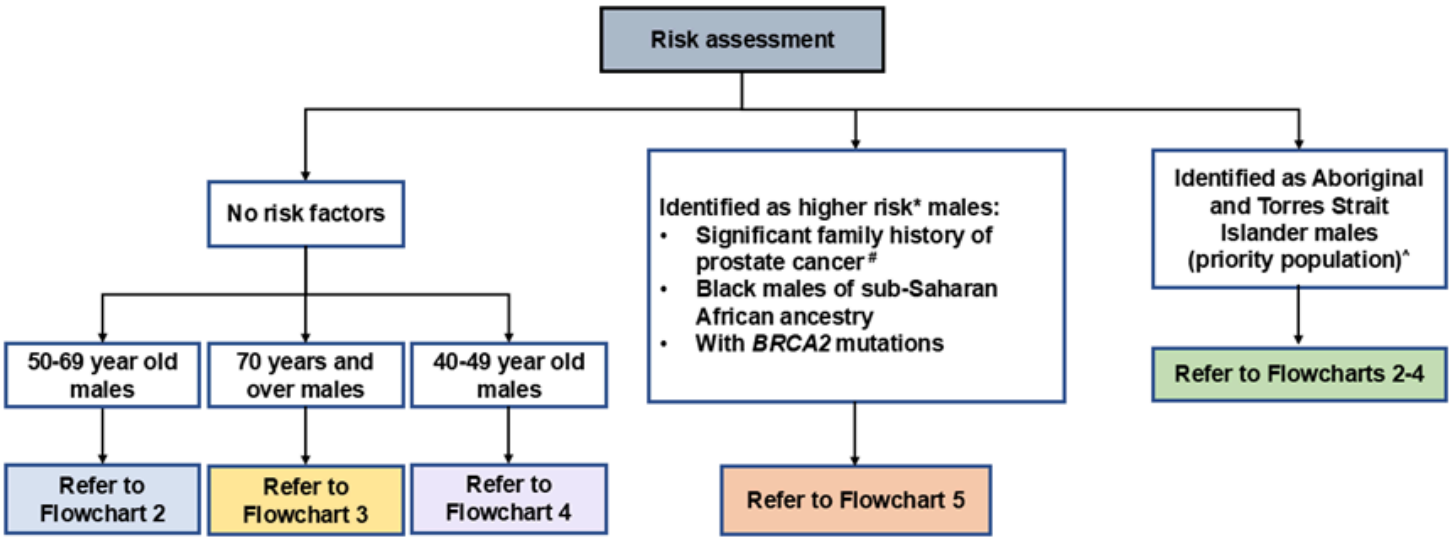
In this review it was not possible to assess all risk factors for clinically significant prostate cancer or prostate cancer specific mortality. This includes but is not limited to family history of breast or ovarian cancer and Lynch Syndrome. We recognise that there may be more risk factors and that they are areas of ongoing research.

For PSA testing recommendations refer to 5. Primary health care setting - PSA testing

Risk assessment flowchart

Flowcharts reflecting the PSA testing recommendations have been developed to aid clinical decision making. Flowchart 1 describes risk assessment for the early detection of prostate cancer in Australia.

Flowchart 1: Risk assessment for the early detection of prostate cancer in Australia



* Higher risk includes but is not restricted to, males with a brother or father diagnosed with prostate cancer, or two second degree relatives diagnosed with prostate cancer, Black males of sub-Saharan African ancestry, and/or confirmed BRCA2 gene mutations (refer 1.1 Family history of prostate cancer). Familial syndromes such as hereditary breast and ovarian cancer and Lynch syndrome are also associated with increased risk of clinically significant prostate cancer compared to the general population.

Significant family history of prostate cancer = a brother diagnosed with prostate cancer, their father diagnosed with prostate cancer before the age of 65, or two or more second degree relatives who died of prostate cancer (refer 1.1 Family history of prostate cancer).

^ PSA testing recommendations for Aboriginal and Torres Strait Islander males are the same as for the general population (refer Section C: Priority populations)

Flowcharts 2-5 can be found in Primary health care setting - PSA testing, describing PSA testing in the primary care setting for:

- 50-69 year old males (Flowchart 2)
- Males 70 years and over (Flowchart 3)
- 40-49 year old males (Flowchart 4)
- Males at higher risk (Flowchart 5)

1.1 Family history of prostate cancer

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? (Clinical Question 1)

Background

Family history of prostate cancer with onset younger than 65 years has been found to be associated with an increased risk of prostate cancer in a number of international cohorts *[5]*. The risk appears to increase with the 'level' of family history, based on factors such as the age at which family members were diagnosed, the relationship (brothers and/or father) and the number of affected relatives. Family history is one of the main risk factors used by health professionals in the Australian primary care setting when assessing risk of prostate cancer and informing men of their risk *[292]*. A number of international guidelines on prostate cancer screening recommend that men with a family history of prostate cancer commence testing for prostate cancer at an earlier age than men not at higher risk of prostate cancer (i.e., men without a family history) *[7]*, *[8]*, *[64]*.

Most guidelines, including the 2016 Australian Guidelines, considered the risks of a diagnosis of any prostate cancer irrespective of prognosis and, in some guidelines, prostate cancer mortality. Since 2016, clinical interest has shifted from risks associated with a diagnosis of any prostate cancer, which includes low-risk potentially indolent disease, to focus on clinically significant prostate cancer. This change in focus is to help reduce harms associated with unnecessary treatment of low stage disease. To minimise potential harms of overtreatment we considered those at "higher risk" as

those at risk of clinically significant prostate cancer or prostate cancer mortality at least double that of the overall risk for the Australian male population. We assessed the risks of these outcomes associated with different family histories.

Strong recommendation

1.1.1 We recommend that males are considered as being at higher risk of prostate cancer mortality for the purposes of PSA testing in the primary care setting if they have significant family history:

- A brother diagnosed with prostate cancer
- Their father was diagnosed with prostate cancer before the age of 65
- Two or more second degree relatives who died of prostate cancer.

In this population the risk of dying from prostate cancer is at least double that of non-higher risk males.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Benefits/desirable effects

Not applicable – this review assessed the magnitude of risks rather than benefits and harms of an intervention.

Harms/ undesirable effects

Two population-based data linkage studies reported the risk of **prostate cancer mortality** associated with different family histories of prostate cancer *[99]*, *[132]*.

In both studies the length of follow-up and the age at which follow-up started varied. Neither provided an estimate of the risk in the control group that took length of follow-up into account; as age at the start of follow-up varied, modelled lifetime risks at a specific age were not appropriate. In the absence of appropriate estimates of risks in the control populations it was not possible to calculate differences in absolute risk or the impact of a specific risk in a specific population.

Instead, the analysis focused on identifying which men were at high or higher risk. Following the approaches used in recent international prostate cancer early detection guidelines *[342]*, *[9]* 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 to the entire male population or those without the risk factor of interest.

Both studies reported the increased risks associated with having a relative or relatives die of prostate cancer *[99]*, *[132]*. The Swedish study *[132]* reported the increased risks associated with having first degree relative/s diagnosed with prostate cancer as well as the increased risk associated with having first degree relative/s who died of prostate cancer. In this study the rankings of the increased risks based on different first-degree relative family histories of prostate cancer diagnosis and prostate cancer death were the same.

In the Swedish cohort *[132]* the risk of prostate cancer mortality for men with a **brother diagnosed with prostate cancer** at any age or their father diagnosed with prostate cancer before 65 years of age was more than double the risk for those without a first degree relative diagnosed with prostate cancer.

In the Utah study *[99]* the risk of prostate cancer mortality associated with having two of more second-degree relatives who have **died of prostate cancer** was more than double the risk for those without a family history of prostate cancer mortality.

Balance of benefits and harms/ desirable and undesirable effects

Not applicable – this review assessed the magnitude of risks rather than the benefits and harms of an intervention.

Certainty of the evidence

Moderate

The certainty of the evidence that men with the following family histories of prostate cancer have **at least double** the risk of prostate cancer mortality is high:

- One or more brothers diagnosed with prostate cancer when compared to those without a first degree relative diagnosed with prostate cancer

- One or more first degree relatives died of prostate cancer when compared to those without a family history of fatal prostate cancer or a first degree relative diagnosed with prostate cancer
- Brother died of prostate cancer when compared to those without a family history of fatal prostate cancer or a first degree relative diagnosed with prostate cancer
- Father and brother diagnosed with prostate cancer when compared to those without a first degree relative diagnosed with prostate cancer
- Two or more second degree relatives but no first-degree relatives who died of prostate cancer when compared to those without a family history of fatal prostate cancer.

The certainty of the evidence that men with the following family histories of prostate cancer have **at least double** the risk of prostate cancer mortality is moderate:

- Father diagnosed with prostate cancer before the age of 65 when compared to those without a first degree relative diagnosed with prostate cancer
- Brother diagnosed with prostate cancer aged 60-64 when compared to those without a first degree relative diagnosed with prostate cancer.

The certainty of the evidence that men with the following family histories of prostate cancer have **less than double** the risk of prostate cancer mortality is moderate:

- One or more second degree relatives but no first-degree relatives who died of prostate cancer when compared to those without a family history of fatal prostate cancer
- Three or more third degree relatives but no first-degree or second-degree relatives who died of prostate cancer when compared to those without a family history of fatal prostate cancer.

Values and preferences

Not applicable as this review only considering the outcome of prostate cancer mortality.

Resources and other considerations

No important issues with the recommended alternative

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

Assessing a patient's risk of prostate cancer mortality by discussing whether there is a family history of prostate cancer would be acceptable to most men and their health providers.

Most men would be comfortable discussing any family history of prostate cancer with their health provider and would want to know if they are at higher risk of prostate cancer mortality as there are actions that can be taken to reduce that risk, e.g. PSA testing.

Health providers would want to know if their patient is at higher risk of prostate cancer mortality as there are steps that they can offer their patient to reduce that risk, e.g. PSA testing.

Feasibility

There are no important barriers likely to limit the feasibility of ascertaining any family history of prostate cancer. It would likely involve a short discussion as to whether any first- or second-degree relatives have been diagnosed with or died of prostate cancer. It is unlikely that this would be burdensome to either the patient or the health provider.

Rationale

This recommendation was informed by two population-based data linkage studies reporting the risks of prostate cancer mortality associated with different family histories of prostate cancer *[99]*, *[132]*. No evidence was found for risks of clinically significant (ISUP Grade ≥ 2) prostate cancer.

The evidence suggests that males whose first-degree relatives (father or brother) have been diagnosed with prostate cancer, or with two or more second degree relatives who have died of prostate cancer, have a higher risk of death from prostate cancer compared to those without a family history. This risk is higher when the family member was diagnosed at an earlier age and if multiple first-degree family members (father or brother) have been diagnosed.

For the recommendations provided in these guidelines, males were considered to be at higher risk of prostate cancer for the purposes of PSA testing, if they had at least double the risk of prostate cancer mortality when compared to those without first degree relatives diagnosed with prostate cancer or no family history of fatal prostate cancer. Those considered higher risk require earlier and more intense PSA testing. See 5. Primary health care setting - PSA testing.

The certainty of the evidence found varied for different family histories. A strong recommendation was made encompassing those family histories for which there was moderate to high certainty evidence for a risk at least double that of the comparator. These were a a brother diagnosed with prostate cancer, their father diagnosed with prostate cancer before the age of 65 or two or more second degree relatives who had died of prostate cancer. For other recommendations regarding risks associated with family history see recommendations 1.1.2 and 1.1.3.

No areas of major debate about the evidence and the recommendations were identified. Recommendations were reached with full consensus.

Clinical question/ PICO

Population: Men with no history of prostate cancer or symptoms that might indicate prostate cancer
Intervention: Exposure: Father and /or brother diagnosed with prostate cancer
Comparator: No first-degree relatives diagnosed with prostate cancer

Summary

One population-based data linkage study *[132]*, compared risks of prostate cancer mortality associated with different family histories of first-degree relatives diagnosed with prostate cancer with no family history of first-degree relatives diagnosed with prostate cancer.

They reported moderate to high certainty evidence that men with the following family histories have at least double the risk of prostate cancer mortality:

- Brother diagnosed with prostate cancer,
- Father diagnosed with prostate cancer before the age of 65.
  In contrast there was low certainty evidence that men with only a father diagnosed aged 65 years or older or at any age had less than double the risk of prostate cancer mortality.

No evidence was found for men with family histories of two or more were second-degree relatives diagnosed with prostate cancer.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No first degree relative diagnosed with prostate cancer	**Intervention** Exposure: Father and /or brother diagnosed with prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 1.81 (CI 95% 1.61, 2.04) Exposure = One first-degree relative – **father** diagnosed with prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**Low** Serious concerns re risk of bias and imprecision	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer may be less than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.06 (CI 95% 0.98, 4.32) Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged less than 60 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		**Moderate** Serious concerns re imprecision.	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer before 60 years of age is probably more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.

Outcome Timeframe	**Study results and measurements**	**Comparator** No first degree relative diagnosed with prostate cancer	**Intervention** Exposure: Father and /or brother diagnosed with prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.55 (CI 95% 1.69, 3.85) Comparator = no first-degree relatives diagnosed with prostate cancer.	Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged 60-64 years*	**Moderate** Serious concerns re imprecision.	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer aged 60-64 years is probably more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 1.97 (CI 95% 1.62, 2.40) Comparator = no first-degree relatives diagnosed with prostate cancer.	Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged 65-74 years*	**Low** Serious concerns re risk of bias and imprecision	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer aged 65-74 years may be less than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 1.67 (CI 95% 1.38, 2.10) Comparator = no first-degree relatives diagnosed with prostate cancer.	Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged 75-82 years*	**Low** Serious concerns re risk of bias and imprecision	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer aged 75-82 years may be less than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 1.63 (CI 95% 1.26, 2.12) Comparator = no first-degree relatives diagnosed with prostate cancer.	Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged over 82 years*	**Low** Serious concerns re risk of bias and imprecision	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer aged over 82 years may be less than double the risk of having no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.75 (CI 95% 2.32, 3.26) Comparator = no first-degree relatives diagnosed with prostate cancer.	Exposure = One first-degree relative – **brother** diagnosed with prostate cancer	**High**	The risk of prostate cancer mortality associated with having a brother diagnosed with prostate cancer is more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 3.27 (CI 95% 2.31, 4.64)		**High**	The risk of prostate cancer mortality associated with having a brother diagnosed with prostate

Outcome Timeframe	**Study results and measurements**	**Comparator** No first degree relative diagnosed with prostate cancer	**Intervention** Exposure: Father and /or brother diagnosed with prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
9 Critical		Exposure = One first-degree relative – **brother** diagnosed with prostate cancer *aged less than 60 years* Comparator = no first-degree relatives diagnosed with prostate cancer.			cancer aged less than 60 years is more than double the risk of having no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.55 (CI 95% 1.89, 3.44) Exposure = One first-degree relative – **brother** diagnosed with prostate cancer *aged 60-64 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		**Moderate** Serious concerns re imprecision	The risk of prostate cancer mortality associated with having a brother diagnosed with prostate cancer aged 60-64 years is probably more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.67 (CI 95% 2.08, 3.43) Exposure = One first-degree relative – **brother** diagnosed with prostate cancer *aged 65-74 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		**High**	The risk of prostate cancer mortality associated with having a brother diagnosed with prostate cancer aged 65-74 years is more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.96 (CI 95% 1.98, 4.43) Exposure = Two first-degree relatives – **father + one brother** diagnosed with prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**High**	The risk of prostate cancer mortality associated with having father and a brother diagnosed with prostate cancer is more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 6.29 (CI 95% 3.79, 10.46) Exposure = Two first-degree relatives – **two brothers** diagnosed with prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**High**	The risk of prostate cancer mortality associated with having two brothers diagnosed with prostate cancer is more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.

Clinical question/ PICO

Population: Men with no history of prostate cancer or symptoms that might indicate prostate cancer

Intervention: Exposure: Family histories of fatal prostate cancer
Comparator: No family history of fatal prostate cancer or no first degree relative diagnosed

Summary

Two population-based data linkage studies were found that reported the risks of prostate cancer mortality associated with different family histories of fatal prostate cancer*[99]*, *[132]*. They used data from the Utah Population Database (UPDB)[99] and the Swedish – Family Cancer Database *[132]*. No evidence was found for risks of clinically significant (ISUP Grade ≥ 2) prostate cancer.

Brandt et al 2010 *[132]* compared risks associated with different family histories of fatal prostate cancer amongst first-degree relatives with those with no family history of first-degree relatives diagnosed with prostate cancer. Albright et al 2017 *[99]* compared risks associated with family histories of fatal prostate cancer amongst first, second, and third-degree relatives with no family history of fatal prostate cancer.

They reported moderate to high certainty evidence that men with the following family histories have at least double the risk of prostate cancer mortality:

- Brother died of prostate cancer,
- Two or more second degree relatives died of prostate cancer.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No family history of of fatal prostate cancer or no first degre	**Intervention** Exposure: Family histories of fatal prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 1.63 (CI 95% 1.32, 2.00) Exposure = Three or more third-degree relatives but no first-degree or second-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**Moderate** Serious concerns re risk of bias	The risk 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 is probably less than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 1.65 (CI 95% 1.50, 1.81) Exposure = one or more second-degree relatives but no first-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**Moderate** Serious concerns re risk of bias	The risk of prostate cancer mortality associated with having one or more second-degree relatives but no first-degree relatives who have died of prostate cancer is probably less than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 2.54 (CI 95% 1.98, 3.20) Exposure = two or more second-degree relatives but no first-degree relatives died of prostate cancer		**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 more than double the risk for

Outcome Timeframe	**Study results and measurements**	**Comparator** No family history of of fatal prostate cancer or no first degre	**Intervention** Exposure: Family histories of fatal prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
		Comparator = no family history of prostate cancer mortality			those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 4.49 (CI 95% 2.24, 8.03) Exposure = three or more second-degree relatives but no first-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having three or more second-degree relatives but no first-degree relatives who have died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 2.49 (CI 95% 2.27, 2.73) Exposure = one first-degree relative died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having one first-degree relative who has died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 3.18 (CI 95% 2.53, 3.94) Exposure = one first-degree relative and one or more second-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having one first-degree relative and one or more second-degree relatives who have died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 5.15 (CI 95% 3.96, 6.59) Exposure = two first-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having two first-degree relatives who have died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 4.63 (CI 95% 3.38, 6.20) Exposure = two first-degree relatives – **two brothers** died of prostate cancer		**High**	The risk of prostate cancer mortality associated with having two brothers who have died of prostate cancer is more than double the risk for those with no

Outcome Timeframe	**Study results and measurements**	**Comparator** No family history of of fatal prostate cancer or no first degre	**Intervention** Exposure: Family histories of fatal prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
9 Critical		Comparator = no family history of prostate cancer mortality			family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 6.86 (CI 95% 2.57, 18.28) Exposure = two first-degree relatives – **father and a brother** died of prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**High**	The risk of prostate cancer mortality associated with having a father and a brother who have died of prostate cancer is more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 1.94 (CI 95% 1.49, 2.50) Exposure = one first-degree relative - **father** died of prostate cancer Comparator = no family history of prostate cancer mortality		**Low** Serious concerns re risk of bias and imprecision	The risk of prostate cancer mortality associated with having a father who has died of prostate cancer may be less than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - 34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.08 (CI 95% 1.80, 2.41) Exposure = one first-degree relative - **father** died of prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer		**Moderate** Serious concerns re imprecision	The risk of prostate cancer mortality associated with having a father who has died of prostate cancer is probably double or more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0 - >40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 2.62 (CI 95% 2.37, 2.89) Exposure = one first-degree relative – **one brother** died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having one brother who has died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.30 (CI 95% 1.38, 3.81) Exposure = one first-degree relative – **one brother** died of prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**Moderate** Serious concerns re imprecision	The risk of prostate cancer mortality associated with having one brother who has died of prostate cancer is probably more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.

Conditional recommendation

1.1.2 We suggest that males should be considered at higher risk of prostate cancer mortality for the purposes of PSA testing if their father was diagnosed with prostate cancer at any age.

In this population the risk of dying from prostate cancer is likely to be more than double that of non-higher risk males.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Benefits/desirable effects

Not applicable – this review assessed the magnitude of risks rather than benefits and harms of an intervention.

Harms/ undesirable effects

Two population-based data linkage studies reported the risk of **prostate cancer mortality** associated with different family histories of prostate cancer *[99]*, *[132]*.

In both studies the length of follow-up and the age at which follow-up started varied. Neither provided an estimate of the risk in the control group that took length of follow-up into account; as age at the start of follow-up varied, modelled lifetime risks at a specific age were not appropriate. In the absence of appropriate estimates of risks in the control populations it was not possible to calculate differences in absolute risk or the impact of a specific risk in a specific population.

Instead, the analysis focused on identifying which men were at high or higher risk. Following the approaches used in recent international prostate cancer early detection guidelines *[342]*, *[9]* 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 to the entire male population or those without the risk factor of interest.

Both studies reported the increased risks associated with having a relative or relatives die of prostate cancer *[99]*, *[132]*. The Swedish study *[132]* reported the increased risks associated with having first degree relative/s diagnosed with prostate cancer as well as the increased risk associated with having first degree relative/s who died of prostate cancer. In this study the rankings of the increased risks based on different first-degree relative family histories of prostate cancer diagnosis and prostate cancer death were the same.

In the Swedish cohort *[132]* the risk of prostate cancer mortality associated with having their father **diagnosed with prostate cancer** at any age was less than double the risk for those without a first degree relative diagnosed with prostate cancer, but at least double the risk if their father died of prostate cancer.

In the Utah study *[99]* the risk of prostate cancer mortality associated with their father having died of prostate cancer was almost double the risk for those without a family history of prostate cancer mortality.

Neither study reported the relative risk of prostate cancer mortality associated with having a family history restricted to two or more second degree relatives diagnosed with prostate cancer.

Balance of benefits and harms/ desirable and undesirable effects

Not applicable – this review assessed the magnitude of risks rather than the benefits and harms of an intervention.

Certainty of the evidence

Low

The certainty of the evidence that men with a family history where only their father was diagnosed with or died of prostate cancer at any age have **less than** or **at least double** the risk of prostate cancer mortality when compared to those without a first degree relative diagnosed with prostate cancer or a family history of fatal prostate cancer is low due to serious concerns regarding risk of bias and imprecision.

Values and preferences

Not applicable as this review only considering the outcome of prostate cancer mortality.

Resources and other considerations

No important issues with the recommended alternative

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

Assessing a patient's risk of prostate cancer mortality by discussing whether there is a family history of prostate cancer would be acceptable to most men and their health providers.

Most men would be comfortable discussing any family history of prostate cancer with their health provider and would want to know if they are at higher risk of prostate cancer mortality as there are actions that can be taken to reduce that risk, e.g. PSA testing.

Health providers would want to know if their patient is at higher risk of prostate cancer mortality as there are steps that they can offer their patient to reduce that risk, e.g. PSA testing.

Feasibility

There are no important barriers likely to limit the feasibility of ascertaining any family history of prostate cancer. It would likely involve a short discussion as to whether any first- or second-degree relatives have been diagnosed with or died of prostate cancer. It is unlikely that this would be burdensome to either the patient or the health provider.

Rationale

This recommendation was informed by two population-based data linkage studies reporting the risks of prostate cancer mortality associated with different family histories of prostate cancer *[99]*, *[132]*. No evidence was found for risks of clinically significant (ISUP Grade ≥ 2) prostate cancer.

The evidence suggests that males with first-degree relatives (father or brother) or two or more second degree relatives who have been diagnosed with or died from prostate cancer have a higher risk of death from prostate cancer compared to those without a first degree relative diagnosed with prostate cancer or a family history of fatal prostate cancer. The risks increase when the family member was diagnosed at an earlier age and if multiple family members have been diagnosed.

For the recommendations provided in these guidelines, males were considered to be at higher risk of prostate cancer for the purposes of PSA testing, if they had at least double the risk of prostate cancer mortality when compared to those without first degree relatives diagnosed with prostate cancer or no family history of fatal prostate cancer. Those considered higher risk require earlier and more intense PSA testing. See 5. Primary health care setting - PSA testing.

There was low certainty conflicting evidence as to whether men whose father but no brothers were diagnosed with or died of prostate cancer at any age, have at least double the risk of prostate cancer mortality when compared to those without a family history of fatal prostate cancer or a first degree relative diagnosed with prostate cancer; the risk with having only their father diagnosed with prostate cancer at any age was less than double the risk for those with no first degree relative diagnosed with prostate cancer whereas the risk associated with having only their father die of prostate cancer was close to or greater than double the risk for those with no family history of fatal prostate cancer or no first degree relative diagnosed with prostate cancer. Neither study compared these risks with those for males without a family history of prostate cancer or the general population; it is possible that the risks would be at least double if the comparator were males with no family history of prostate cancer or the general population. Consequently, for the purposes of PSA testing, we have taken a conservative approach and made a conditional recommendation that these males be considered higher risk.

We found high certainty evidence for a family history of two more second-degree relatives dying of prostate cancer but did not find evidence for a family history of two or more second-degree relatives diagnosed with prostate cancer. As the rankings of the increased risks based on different first-degree relative family histories of prostate cancer diagnosis and prostate cancer death were the same in the Swedish study, we have taken a conservative approach and made a consensus-based recommendation suggesting that males with second-degree relative who have been diagnosed with prostate cancer are likely to be at higher risk of the disease (see recommendation 1.1.3)

No areas of major debate about the evidence and the recommendations were identified. Recommendations were reached with full consensus.

Clinical question/ PICO

Population: Men with no history of prostate cancer or symptoms that might indicate prostate cancer
Intervention: Exposure: Father and /or brother diagnosed with prostate cancer
Comparator: No first-degree relatives diagnosed with prostate cancer

Summary

One population-based data linkage study *[132]* compared risks of prostate cancer mortality associated with different family histories of first-degree relatives diagnosed with prostate cancer with no family history of first-degree relatives diagnosed with prostate cancer. This study provided low certainty evidence that men with only a father diagnosed aged 65 years or older or at any age had less than double the risk of prostate cancer mortality. No evidence was found for men with family histories of two or more were second-degree relatives diagnosed with prostate cancer.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No first degree relative diagnosed with prostate cancer	**Intervention** Exposure: Father and /or brother diagnosed with prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 1.81 (CI 95% 1.61, 2.04) Exposure = One first-degree relative – **father** diagnosed with prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**Low** Serious concerns re risk of bias and imprecision	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer may be less than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.06 (CI 95% 0.98, 4.32) Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged less than 60 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		**Moderate** Serious concerns re imprecision.	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer before 60 years of age is probably more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.55 (CI 95% 1.69, 3.85) Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged 60-64 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		**Moderate** Serious concerns re imprecision.	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer aged 60-64 years is probably more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 1.97 (CI 95% 1.62, 2.40) Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged 65-74 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		**Low** Serious concerns re risk of bias and imprecision	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer aged 65-74 years may be less than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths	Based on data from 3,900,000 participants in 1	Measured by: Hazard ratio 1.67 (CI 95% 1.38, 2.10)		**Low** Serious concerns re risk of bias and	The risk of prostate cancer mortality associated with having a father diagnosed

Outcome Timeframe	**Study results and measurements**	**Comparator** No first degree relative diagnosed with prostate cancer	**Intervention** Exposure: Father and /or brother diagnosed with prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
Variable time frame 0-34 years 9 Critical	studies.	Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged 75-82 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		imprecision	with prostate cancer aged 75-82 years may be less than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 1.63 (CI 95% 1.26, 2.12) Exposure = One first-degree relative – **father** diagnosed with prostate cancer *aged over 82 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		**Low** Serious concerns re risk of bias and imprecision	The risk of prostate cancer mortality associated with having a father diagnosed with prostate cancer aged over 82 years may be less than double the risk of having no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.75 (CI 95% 2.32, 3.26) Exposure = One first-degree relative – **brother** diagnosed with prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**High**	The risk of prostate cancer mortality associated with having a brother diagnosed with prostate cancer is more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 3.27 (CI 95% 2.31, 4.64) Exposure = One first-degree relative – **brother** diagnosed with prostate cancer *aged less than 60 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		**High**	The risk of prostate cancer mortality associated with having a brother diagnosed with prostate cancer aged less than 60 years is more than double the risk of having no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.55 (CI 95% 1.89, 3.44) Exposure = One first-degree relative – **brother** diagnosed with prostate cancer *aged 60-64 years* Comparator = no first-degree relatives diagnosed with prostate cancer.		**Moderate** Serious concerns re imprecision	The risk of prostate cancer mortality associated with having a brother diagnosed with prostate cancer aged 60-64 years is probably more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.67 (CI 95% 2.08, 3.43)		**High**	The risk of prostate cancer mortality associated with having a brother diagnosed with prostate cancer aged 65-74 years is more than double the risk

Outcome Timeframe	**Study results and measurements**	**Comparator** No first degree relative diagnosed with prostate cancer	**Intervention** Exposure: Father and /or brother diagnosed with prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
9 Critical		Exposure = One first-degree relative – **brother** diagnosed with prostate cancer *aged 65-74 years* Comparator = no first-degree relatives diagnosed with prostate cancer.			for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.96 (CI 95% 1.98, 4.43) Exposure = Two first-degree relatives – **father + one brother** diagnosed with prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**High**	The risk of prostate cancer mortality associated with having father and a brother diagnosed with prostate cancer is more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 6.29 (CI 95% 3.79, 10.46) Exposure = Two first-degree relatives – **two brothers** diagnosed with prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**High**	The risk of prostate cancer mortality associated with having two brothers diagnosed with prostate cancer is more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.

Clinical question/ PICO

Population: Men with no history of prostate cancer or symptoms that might indicate prostate cancer
Intervention: Exposure: Family histories of fatal prostate cancer
Comparator: No family history of fatal prostate cancer or no first degree relative diagnosed

Summary

Two population-based data linkage studies were found that reported the risks of prostate cancer mortality associated with different family histories of lethal prostate cancer*[99]*, *[132]*. They used data from the Utah Population Database (UPDB)[99] and the Swedish – Family Cancer Database *[132]*. No evidence was found for risks of clinically significant (ISUP Grade ≥ 2) prostate cancer.

Brandt et al 2010 *[132]* compared risks associated with different family histories of first-degree relatives who were diagnosed with or died of prostate cancer with no family history of first-degree relatives diagnosed with prostate cancer. Albright et al 2017 *[99]* compared risks associated with family histories of fatal prostate cancer amongst first, second, and third-degree relatives with no family history of fatal prostate cancer.

For men with a father but no other relatives who had died of prostate cancer the risk of prostate cancer mortality was just less than double that for men with no family history of fatal prostate cancer *[99]* but just greater than double that for men with no family history of first-degree relatives diagnosed with prostate cancer *[132]*. The certainty of this evidence was low.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No family history of of fatal prostate cancer or no first degre	**Intervention** Exposure: Family histories of fatal prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 1.63 (CI 95% 1.32, 2.00) Exposure = Three or more third-degree relatives but no first-degree or second-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**Moderate** Serious concerns re risk of bias	The risk 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 is probably less than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 1.65 (CI 95% 1.50, 1.81) Exposure = one or more second-degree relatives but no first-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**Moderate** Serious concerns re risk of bias	The risk of prostate cancer mortality associated with having one or more second-degree relatives but no first-degree relatives who have died of prostate cancer is probably less than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 2.54 (CI 95% 1.98, 3.20) Exposure = two or more second-degree relatives but no first-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**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 more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 4.49 (CI 95% 2.24, 8.03) Exposure = three or more second-degree relatives but no first-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having three or more second-degree relatives but no first-degree relatives who have died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 2.49 (CI 95% 2.27, 2.73) Exposure = one first-degree relative died of prostate cancer		**High**	The risk of prostate cancer mortality associated with having one first-degree relative who has died of prostate cancer is more

Outcome Timeframe	**Study results and measurements**	**Comparator** No family history of of fatal prostate cancer or no first degre	**Intervention** Exposure: Family histories of fatal prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
9 Critical		Comparator = no family history of prostate cancer mortality			than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 3.18 (CI 95% 2.53, 3.94) Exposure = one first-degree relative and one or more second-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having one first-degree relative and one or more second-degree relatives who have died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 5.15 (CI 95% 3.96, 6.59) Exposure = two first-degree relatives died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having two first-degree relatives who have died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 4.63 (CI 95% 3.38, 6.20) Exposure = two first-degree relatives – **two brothers** died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having two brothers who have died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 6.86 (CI 95% 2.57, 18.28) Exposure = two first-degree relatives – **father and a brother** died of prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**High**	The risk of prostate cancer mortality associated with having a father and a brother who have died of prostate cancer is more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0 - > 40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 1.94 (CI 95% 1.49, 2.50) Exposure = one first-degree relative - **father** died of prostate cancer Comparator = no family history of prostate cancer mortality		**Low** Serious concerns re risk of bias and imprecision	The risk of prostate cancer mortality associated with having a father who has died of prostate cancer may be less than double the risk for those with no family history of prostate cancer mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** No family history of of fatal prostate cancer or no first degre	**Intervention** Exposure: Family histories of fatal prostate cancer	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths Variable time frame 0 - 34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.08 (CI 95% 1.80, 2.41) Exposure = one first-degree relative - **father** died of prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer		**Moderate** Serious concerns re imprecision	The risk of prostate cancer mortality associated with having a father who has died of prostate cancer is probably double or more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.
Prostate cancer-specific deaths Variable time frame 0 - >40 years 9 Critical	Based on data from 686,203 participants in 1 studies.	Measured by: Risk ratio 2.62 (CI 95% 2.37, 2.89) Exposure = one first-degree relative – **one brother** died of prostate cancer Comparator = no family history of prostate cancer mortality		**High**	The risk of prostate cancer mortality associated with having one brother who has died of prostate cancer is more than double the risk for those with no family history of prostate cancer mortality.
Prostate cancer-specific deaths Variable time frame 0-34 years 9 Critical	Based on data from 3,900,000 participants in 1 studies.	Measured by: Hazard ratio 2.30 (CI 95% 1.38, 3.81) Exposure = one first-degree relative – **one brother** died of prostate cancer Comparator = no first-degree relatives diagnosed with prostate cancer.		**Moderate** Serious concerns re imprecision	The risk of prostate cancer mortality associated with having one brother who has died of prostate cancer is probably more than double the risk for those with no first-degree relatives diagnosed with prostate cancer.

Consensus recommendation

1.1.3 We propose that males should be considered at higher risk of prostate cancer mortality for the purposes of PSA testing if two or more second degree relatives (uncle, grandfather, etc.) were diagnosed with prostate cancer.

In this population the risk of dying from prostate cancer is likely to be more than double that of non-higher risk males.

Review by 2030, subject to emerging evidence

Rationale

We found high certainty evidence for a family history of two or more second-degree relatives dying of prostate cancer but did not find evidence for a family history of two or more second-degree relatives diagnosed with prostate. As the rankings of the increased risks based on different first-degree relative family histories of prostate cancer diagnosis and prostate cancer death were the same in the Swedish study, we have taken a conservative approach and made a consensus-based recommendation suggesting that males with second-degrees relative who have been diagnosed with prostate cancer are likely to be at higher risk of the disease.

No areas of major debate about the evidence and the recommendations were identified. Recommendations were reached with full consensus.

1.2 Black males of sub-Saharan African ancestry living in Australia

Clinical question

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? (Clinical question 2)

Background

Internationally, Black males of sub-Saharan African ancestry have a disproportionate prostate cancer burden. Relative to Caucasian males, males of black sub-Saharan ancestry have a two-fold higher risk of death from prostate cancer and are more likely to be diagnosed with prostate cancer at an earlier age. They have increased risk of being diagnosed with metastatic disease, with prostate cancer specific mortality three to nine years earlier than the general population *[167]*. These increased risks are likely to be due to socioeconomic factors as well as genetic predisposition *[318]*.

Little is known about whether Black males with sub-Saharan ancestry, living in Australia face similar risks. It is thought that the risk profile for Black males of sub-Saharan ancestry living in Australia may be comparable to that reported in the Americas and Europe.

Evidence – systematic review

A systematic review was carried out to determine the relative risk of clinically significant prostate cancer or prostate cancer-specific mortality for Black males of sub-Saharan African ancestry who are living in Australia. No relevant studies were found and no relevant data for this population was found on the Australian Institute of Health and Wellbeing website.

More information can be found in the Technical Report.

Evidence – Advisory Group report

Evidence from our systematic review was insufficient to draft recommendations on the prostate cancer risks for Black males of sub-Saharan ancestry living in Australia. However, in other countries, including Africa, the United States, Canada, the United Kingdom and the Caribbean, there is evidence to suggest that these males are at higher risk of being diagnosed with clinically significant prostate cancer and dying from it. We undertook a literature review to further understand this risk and how it might impact black males with sub-Saharan ancestry who live in Australia.

More information can be found in Appendix 3: Literature reviews - Men of African descent advisory group report.

Consensus recommendation

1.2.1 We propose that Black males of sub-Saharan ancestry be considered at higher risk of clinically significant prostate cancer.

Review by 2030, subject to emerging evidence

Rationale

This recommendation was drafted based on evidence from international data as our systematic review of the literature did not identify suitable publications or data reporting the risks of clinically significant prostate cancer or prostate cancer mortality for black males of sub-Saharan ancestry living in Australia.

It is reported that black males of sub-Saharan ancestry living in the Americas and Europe, have a two-fold higher risk of being diagnosed with prostate cancer before the age of 45 than white males *[30]*, *[32]*, *[261]*. They have a higher risk of being diagnosed with clinically significant prostate cancer and are often diagnosed with advanced cancer thus increasing their risk of metastasis and early death *[178]*, *[235]*, *[339]*, *[243]*, *[32]*, *[31]*.

Australia has a growing population of black males of sub-Saharan ancestry who may be at higher risk of prostate cancer for whom early detection has the potential to save lives *[29]*.

No areas of major debate about the evidence and the recommendations were identified. Recommendations were reached with full consensus.

More information can be found in Appendix 3: Literature reviews - Men of African descent advisory group report.

Clinical question/ PICO

Population: Individuals in Australia at risk of prostate cancer without a prostate cancer diagnosis or symptoms that might indicate prostate cancer.

Intervention: Exposure: sub-Saharan African ancestry

Comparator: Ancestry other than sub-Saharan African or Australian

Summary

A systematic review was carried out to determine the relative risk of clinically significant prostate cancer or prostate cancer-specific mortality for black males of sub-Saharan African ancestry who are living in Australia. No relevant studies were found and no relevant data for this population was found on the Australian Institute of Health and Wellbeing website.

More information can be found in the Technical report.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** Exposure: sub-Saharan African ancestry	**Certainty of the evidence** (Quality of evidence)
Prostate cancer mortality		No studies identified		
Clinically significant prostate cancer		No studies identified		

Key message

1.2.2 To best support Black males of sub-Saharan African ancestry, development and implementation of targeted, culturally appropriate health promotion/education campaigns are needed to increase awareness of prostate cancer and risk.

Review by 2030, subject to emerging evidence

1.3 Germline mutations

Background

Although germline mutations, including *BRCA2*, have not been specific topics of this review, there is evidence to indicate that males with a *BRCA2* gene mutation should be considered at high risk of clinically significant prostate cancer and death from prostate cancer.

BRCA2 mutations and prostate cancer risk

- Relative risk 2.5 to 4.6
- Relative risk 8 to 23 prostate cancer at 55 years or under
- *BRCA2* germline alteration is an independent predictor of metastases and worse prostate cancer specific survival

Source - Table 3.2, page 14. EAU Guidelines. Edn. presented at the EAU Annual Congress Madrid 2025. ISBN 978-94-92671-29-5.

Refer to the European Association of Urology guidelines for further information.

Good practice statement

1.3.1 Consider males with a *BRCA2* mutation as higher risk.

Review by 2030, subject to emerging evidence

Rationale

Based on the evidence considered for EAU guidelines 2025 such as that provided by Nyberg et al 2020 *[355]*, it is accepted that those with a *BRCA2* mutation have over double the risk of prostate cancer mortality when compared to the general population.

For PSA testing recommendations refer to Primary health care setting - PSA testing.

1.4 Other risk factors

There are multiple other factors associated with risk of clinically significant prostate cancer or death from prostate cancer including: rural and remote place of residence, metabolic syndrome, diet, smoking, and industrial exposures.

Refer Section C: Priority populations)

Good practice statement

1.4.1 Familial syndromes such as hereditary breast and ovarian cancer and Lynch Syndrome are also associated with increased risk of clinically significant prostate cancer compared to the general population.

Review by 2030, subject to emerging evidence

Rationale

Familial syndromes including hereditary breast and ovarian cancer and Lynch syndrome are considered risk factors for prostate cancer *[356]*, *[357]*, *[358]*. The EAU guidelines and the AUA guidelines highlight the importance of these factors as a risk factor for prostate cancer *[390]*, *[167]*.

Section B: Decision support

2. Decision support

Background

All patients have the right to make informed decisions about their health and to understand the information and recommendations they receive from their healthcare providers *[29]*, *[111]*. For the purposes of these Guidelines, 'decision support' refers to communication and collaboration between clinicians and patients to make a health-related decision. This includes integrating a patient's priorities and healthcare preferences with the best available information about the benefits and possible harms of the available options to reach a decision *[169]*. Decision support is particularly useful where choices are sensitive to a patient's preferences, more than one reasonable option is available, or where the ratio of benefits to harms is uncertain *[207]*, *[245]*.

In this section the Guidelines consider current best clinical practice approaches to, and consumer preferences for, decision support in the context of a planned program for the early detection of prostate cancer in Australia. Hence, recommendations were informed by the:

- Australian Commission on Safety and Quality in Health Care, National Safety and Quality Primary and Community Healthcare Standards *[111]*
- The Royal Australian College of General Practitioners, Standards for General Practices (5th edn)*[294]*
- Findings of Public Consultation *[204]* (refer Dissemination Report: Public consultation findings)

Good practice statement

2.1 Offer decision support in accordance with current best practice. Approaches to decision support should take into account personal preferences and circumstances.

Decision support is more likely to be required in circumstances where there are alternative management options.

Decision support approaches can include:

- Informal discussions phrased in terms of options and potentially a recommendation
- In-depth discussions explaining benefits, potential harms and timelines of testing
- Provision of general written information, and/or provision of decision support tools
- Referral to digital resources such as websites or apps from reputable organisations.

Review by 2030, subject to emerging evidence

Rationale

Masculinity

Gender is a social determinant of health where traditional masculine norms are routinely associated with men's low engagement with health care services *[306]*. Reflecting this, systematic reviews of men's perspectives about prostate cancer screening consistently describe masculinity as a potential barrier to communication about prostate cancer and to men seeking medical advice for prostate cancer concerns *[217]*, *[214]*, *[170]*. Men-centred care considers how health care services for men intersect with masculinity and delivers care that is tailored to match up with, or connect to, the perspectives and needs of the man as an individual. In primary health care this includes communication strategies, the structure of the clinical intervention, and the therapeutic or clinical alliance *[306]*.

Approaches that have been described as critical for a successful prostate cancer testing discussion include using everyday language, the man receiving a sufficient quantity of information, spending enough time, and having a trusting relationship with the clinician *[182]*. With regards to the clinical relationship, some men have an expectation that their doctor will initiate and make recommendations about testing for prostate cancer and that a strong relationship with their doctor allows them to gain decisional confidence *[214]*.

Information Seeking

In the context of cancer risk reduction and screening, some men will be active information-seekers while others may be passive information-gatherers *[297]*. The Internet is the primary information source for men who are active information seekers, with men also seeking information from their social networks *[297]*. For men who are passive information gatherers, unsolicited advice from healthcare providers is the primary source of information, with information also gathered from social networks and the mass media *[297]*. Men preferred gender and age-specific information presented in a practical, factual, simple, and direct approach *[297]*.

Levels of decision support

Men will have different preferences and needs for decision support. Decision support offered must be tailored to the individual, depending on their values, what they want to know, and how involved they would like their healthcare provider to be in making their decision *[182]*, *[228]*, *[230]*.

However, the degree of detail and healthcare provider involvement in decision making may vary according to the man's preferences.

Levels of decision support may include *[170]*, *[182]*, *[228]*, *[230]*, *[176]*, *[268]*:

- **Brief information – brief interaction**: a short discussion of the purpose of prostate cancer testing, benefits of early detection of prostate cancer, benefits and possible harms of prostate cancer testing, and whether the man would like to participate in testing. The man may have already made a decision in relation to testing prior to the consultation and inform their provider without wish for further discussion *[170]*, *[182]*.
  - This can occur opportunistically during contacts addressing other healthcare needs and may be limited to introducing the concept of prostate cancer testing.
- **Moderate information – moderate interaction**: for men wanting more information or more involvement of their healthcare provider in the decision making process, a discussion may be held allowing time for men to request further information, discuss the benefits and possible harms specific to their risk profile or ask for a recommendation from their healthcare provider. Additional written, digital or other resources may be useful and can improve men's knowledge about testing for prostate cancer *[268]*. The man may be uncertain about testing, wish to verify information from other sources or seek the opinion of their healthcare provider.
  - This may occur opportunistically if time allows in other consultations, or in specifically organised consultations.
- **Greater information – greater interaction**: men who are unsure or anxious about testing may wish for more detailed information and greater input from their healthcare provider when making the decision. Additional written, digital or other resources may be useful to improve men's knowledge about testing for prostate cancer *[268]*. A more structured approach to decision making and use of decision aids may support men who are uncertain or concerned about testing.
  - A more comprehensive discussion is likely to require a specifically organised consultation.

Decision aids explaining what the decision is, the options available, and the potential benefits and harms can help patients become more knowledgeable, better understand risk, and make more informed decisions *[316]*; including those from underserved populations *[164]*.

Additional information about decision support is available from the websites below.

- ACSQHC Resources for shared decision making (clinician and consumer) https://www.safetyandquality.gov.au/our-work/partnering-consumers/shared- decision making
- Choosing Wisely Australia (ACSQHC hosted initiative for clinicians, consumers and health services) https://www.choosingwisely.org.au/
- Ask Share Know https://askshareknow.org.au/
- Shared decision making with Aboriginal and Torres Strait Islander people https://aci.health.nsw.gov.au/shared- decision making
- International Patient Decision Aid Standards: https://decisionaid.ohri.ca/IPDAS/

Section C: Priority populations

In developing these implementation priorities, the Review recognises the diversity of the Australian population and the cultures, traditions, beliefs and values of these communities. Further, these groups may experience additional barriers to engagement with healthcare that impact their health outcomes. Priority populations for the early detection of prostate cancer in Australia may include:

- Aboriginal and Torres Strait Islander people
- LGBTIQA+ populations
- Culturally and linguistically diverse communities (including Black men of sub-Saharan African ancestry), and
- People living in rural and remote areas.

By working collaboratively with communities to build solutions and resources that meet their specific needs, we can support early detection of prostate cancer and improve health outcomes for these populations. Refer Dissemination Plan for detailed implementation and research priorities for priority populations.

3.1 Aboriginal and Torres Strait Islander males

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 people compared with the risks for the those who do not, overall and by age groups? (Clinical question 3)

Background

We have consulted extensively with Aboriginal and Torres Strait Islander community members and content experts and sought guidance on the naming protocols used in the preparation of the Guidelines. We respectfully use the phrase Aboriginal and Torres Strait Islander males throughout this Guideline in accordance with the guidance received.

There is no evidence regarding the elevated risk of developing clinically significant prostate cancer for Aboriginal and Torres Strait Islander males. However, if diagnosed with prostate cancer, survival outcomes in Aboriginal and Torres Strait Islander males are worse than the non-Indigenous male population. Aboriginal and Torres Strait Islander males are therefore considered a priority population in the context of a planned testing program for the early detection of prostate cancer.

Aboriginal and Torres Strait Islander males face significant health disparities, particularly in cancer outcomes. Colonisation has eroded traditional cultural practices, impacting their health and well-being. Aboriginal and Torres Strait Islander males have higher cancer burdens and lower participation in health screenings compared to non-Indigenous men *[323]*, *[158]*. As for all Australian males, prostate cancer is the most common cancer among Aboriginal and Torres Strait Islander males. Compared with non-Indigenous men, Aboriginal and Torres Strait Islander males have a lower disease incidence but lower prostate cancer survival rates *[65]*. It is unclear if these differences are due to increased risk of lethal prostate cancer in this population or low levels of PSA testing.

To address this clinical question and draft recommendations, we undertook a systematic review and a broader detailed literature review. We also undertook extensive consumer consultation and contextual analysis.

For PSA testing recommendations refer to Primary health care setting - PSA testing.

For Guideline implementation and monitoring information and key messages refer to Section F: Guideline implementation and monitoring.

Key messages

3.1.1

PSA testing should be embedded into the Aboriginal and Torres Strait Islander annual health assessment program.

3.1.2

Through programs such as the Medical Specialist Outreach Assistance Program (MSOAP), existing telehealth infrastructure, and point of care testing for PSA in Aboriginal Community Controlled Health Organisations, Aboriginal and Torres Strait Islander males, particularly in rural and remote communities, have facilitated access to specialist diagnostic and management services once they are identified as at-risk. These existing infrastructures can be utilised to support males undergoing PSA testing who require further testing/care.

3.1.3

To further support Aboriginal and Torres Strait Islander males, development and implementation of targeted, culturally appropriate health promotion/education campaigns are needed to reduce stigma around testing and increase awareness of prostate cancer. These programs should commence early and run in parallel with the Aboriginal and Torres Strait Islander annual health assessment program.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Benefits/desirable effects

Not applicable - assessing the magnitude of risks rather than assessing the benefits and harms of an intervention.

Harms/undesirable effects

Based on a single set of data the risk of prostate cancer mortality for men who identify as Aboriginal and Torres Strait Islander did not differ from the risk seen amongst those who did not *[89]*.

In a single study in the pre-PSA testing era, the risk of prostate cancer mortality for men who identify as Aboriginal living in remote or rural communities in Queensland did not differ from the risk seen amongst the Queensland male population *[152]*.

No evidence was found for the risks of clinically significant disease.

Balance of benefits and harms/desirable and undesirable effects

Not applicable - assessing magnitude of risks rather than assessing benefits and harms of an intervention.

Certainty of the evidence

Very low

The certainty of the evidence for similar rates of prostate cancer mortality for men who identify as Aboriginal and Torres Strait Islander and those who do not is low as there were serious concerns regarding risk of bias primarily because the analyses did not take into account important confounders such as socioeconomic status and life expectancy.

The certainty of the evidence for similar rates of prostate cancer mortality for men who identify as Aboriginal living in remote or rural communities in Queensland and all men living in Queensland is very low as the analyses did not take into account the important confounders, socioeconomic status and life expectancy, plus there are serious concerns regarding indirectness as the study was undertaken over 25 years ago *[152]*.

The finding that men who identify as Aboriginal and Torres Strait Islander were not at higher risk of prostate cancer mortality was unexpected as they have poorer survival outcomes if diagnosed with prostate cancer and it is likely they have lower PSA testing rates supporting concerns that the results may be highly distorted by confounding.

Values and preferences

Not applicable as no evidence was found that men who identify as Aboriginal or Torres Strait Islander are at higher risk of prostate cancer mortality or clinically significant prostate cancer.

Resources and other considerations

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

Not applicable as no evidence was found that men who identify as Aboriginal or Torres Strait Islander are at higher risk of prostate cancer mortality or clinically significant prostate cancer.

Feasibility

Not applicable as no evidence was found that men who identify as Aboriginal or Torres Strait Islander are at higher risk of prostate cancer mortality or clinically significant prostate cancer.

Rationale

There is no evidence regarding an elevated risk of developing clinically significant prostate cancer or prostate cancer mortality for Aboriginal and Torres Strait Islander males, however, if diagnosed with prostate cancer, survival outcomes in Aboriginal and Torres Strait Islander males are worse than the general Australian male population. Aboriginal and Torres Strait Islander males are therefore considered a priority population in the context of a planned testing program for the early detection of prostate cancer.

No areas of major debate about the evidence and the recommendations were identified. Recommendations were reached with full consensus.

More information can be found in Appendix 3: Literature Reviews - Aboriginal and Torres Strait Islander populations advisory group report.

Clinical question/ PICO

Population: Men in Australia at risk of prostate cancer without a prostate cancer diagnosis or symptoms that might indicate prostate cancer
Intervention: Men who identify as Aboriginal or Torres Strait Islander
Comparator: Men who do not identify as Aboriginal or Torres Islander or the Australian male population

Summary

One study met the systematic review criteria *[152]* This study examined cancer incidence and mortality in remote Indigenous communities in rural Queensland. Relevant data was also found in data files accompanying the Australian Institute of Health and Wellbeing (AIHW) report *[89]* They provided evidence on prostate cancer mortality for men who identify as Aboriginal and Torres Strait Islander relative to those who do not or the general Australian male population.

Their results suggested that men who identify as Aboriginal and Torres Strait Islander males may not be at higher risk of prostate cancer mortality than those that do not or the Australian male population. The certainty of evidence was low to very low due to serious concerns regarding bias and indirectness.

No evidence was found for the outcome of clinically significant (ISUP grade ≥ 2) prostate cancer.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** Not Aboriginal or Torres Islander or all Australian men	**Intervention** Aboriginal or Torres Strait Islander	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths Exposed = men who identify as Aboriginal and Torres Strait Islander in NSW, QLD, NT, WA and SA 5 years 9 Critical	Measured by: Standardised mortality rate ratio Based on data from participants in 1 studies.	 **25.3** per 100,000 Difference:	**24.5** per 100,000 **SMD 1 fewer** (CI 95% 11 fewer — 18 more)	**Low** Downgraded by two levels due to very serious concerns re risk of bias	Men who identify as Aboriginal and Torres Strait Islander may not be at higher risk of prostate cancer mortality when compared with men who do not.
Prostate cancer-specific deaths Exposed = Men who identify as Aboriginal living in rural and remote communities in QLD 15 years 9 Critical	Measured by: Standardised mortality rate ratio Based on data from participants in 1 studies.	**44** per 100,000 Difference:	**47** per 100,000 **SMD 3 more** (CI 95% 27 fewer — 59 more)	**Very low** Downgraded by three levels due to very serious concerns re risk of bias and serious concerns re indirectness	We are uncertain as to whether the risk of prostate cancer mortality is no different for men who identify as Aboriginal living in remote and rural Indigenous communities in Queensland when compared with the male population of Queensland.
Diagnosis of clinically significant		No Evidence found			

Outcome Timeframe	**Study results and measurements**	**Comparator** Not Aboriginal or Torres Islander or all Australian men	**Intervention** Aboriginal or Torres Strait Islander	**Certainty of the evidence** (Quality of evidence)	**Summary**
prostate cancer 9 Critical					

References

89. Australian Institute of Health and Welfare 2024. Aboriginal and Torres Strait Islander Health Performance Framework: summary report August 2024. AIHW: Australian Government. [Accessed 27 November 2024].

152. Coory M, Thompson A, Ganguly I. Cancer among people living in rural and remote Indigenous communities in Queensland. Medical Journal of Australia 2000;173(6):301-304

3.2 Other priority populations

Background

There are multiple other factors associated with risk of clinically significant prostate cancer or death from prostate cancer including but not limited to: industrial exposure; smoking; rural and remote place of residence and; socioeconomic status. Further, baseline PSA values for transgender women on gender-affirming hormones may be artificially lower, necessitating extra care when interpreting PSA. Currently, however, evidence for these priority groups in Australia is limited and further research is outside the scope of this review.

While there is emerging evidence regarding risks of clinically significant prostate cancer or prostate cancer death in priority populations, data are not available to make specific testing recommendations. For recommendations on further research for priority populations including: rural and remote communities; migrant groups; culturally and linguistically diverse (CALD) communities; LGBTIQA+ populations; people with disability; military veterans and prisoners.

Refer Appendix 3: Literature Review - Social determinants of prostate cancer and early detection of prostate cancer in Australia.

Refer Section F: Guideline implementation and monitoring

Refer Dissemination report for research priorities

Section D: Early detection

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? (Clinical question 4)

Background

A digital rectal examination (DRE) is a simple physical procedure used to examine the lower rectum and other internal organs including the prostate. Prior to PSA testing and systematic prostate biopsy, DRE in combination with serum prostatic acid phosphates was routinely used for establishing the clinical suspicion of prostate cancer. However, men were often reluctant to have a DRE *[11]* and concerns over DRE testing have been reported to discourage men from undergoing PSA testing *[12]*. Other problems with DRE are that a significant volume of cancer needs to be present before a DRE abnormality can be detected and significant observer variation has been noted *[13]*, *[14]*.

The 2016 Guidelines *[1]* noted that with PSA testing being increasingly offered to men concerned about the possibility of prostate cancer, with the aim of identifying much smaller foci of cancer, it is important to ask whether DRE still has an important role in the detection of asymptomatic prostate cancer in the primary care setting. This question remains relevant today, particularly with changes in clinical practice, expert opinion and the increased use of sophisticated imaging technology (mpMRI) in combination with PSA testing for early detection of prostate cancer in asymptomatic individuals.

The current recommendations are a result of reviewing and updating the systematic review undertaken for the 2016 guidelines. As clinical interest has shifted from any prostate cancer to clinically significant prostate cancer to reduce harms associated with overtreatment, and reference standards for diagnostic accuracy studies have improved, we have narrowed the previous selection criteria to focus on:

- 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 µg/L was considered directly relevant to the clinical question as the current guidelines recommend a total PSA threshold of 3.0 µg/L.

Conditional recommendation against

4.1 We suggest that digital rectal examination not be offered in the primary care setting as a routine addition to PSA testing and risk assessment.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Benefits/desirable effects

In a single study of men in the primary care setting *[17]*, if the prevalence of clinically significant disease is either 5% or 10%, the increase in the detection of clinically significant prostate cancer with the addition of DRE to PSA testing using a threshold of 4.0 µg/L is trivial (clinically unimportant).

Harms/undesirable effects

In a single study of men in the primary care setting *[17]*, if the prevalence of clinically significant disease is either 5% or 10%, the increase in unnecessary referrals for further investigation with the addition of DRE to PSA testing using a threshold of 4.0 µg/L is trivial (clinically unimportant).

Balance of benefits and harms/desirable and undesirable effects

The reported number of additional unnecessary referrals for further investigation to detect an additional clinically significant cancer is dependent on the prevalence of clinically significant prostate cancer.

In three studies *[15]*, *[16]*, *[18]* only those who were test positive underwent biopsy. As a result for these studies, sensitivity and specificity could not be calculated and applied to different prevalences, and the prevalence of clinically significant prostate cancer was unknown, rendering their results difficult to interpret and apply.

In the fourth study *[17]* all men regardless of their test results underwent biopsy enabling the calculation of sensitivity and specificity and the calculation of the number of additional unnecessary referrals for further investigation (harms) per additional clinically significant prostate cancer detected (benefit) for a specific prevalence of clinically important prostate cancer. Based on the results of this study, if the prevalence of clinically significant prostate cancer is 5%, the number of unnecessary referrals for further investigation with the addition of DRE to PSA testing using a threshold of 4.0 µg/L would be 11.0 and if the prevalence of clinically significant prostate cancer is 10%, the number of unnecessary referrals for further investigation with the addition of DRE to PSA testing using a threshold of 4.0 µg/L would be 4.9.

Certainty of the evidence

Very low

The certainty of the evidence was rated very low due to elevated risks of bias due to inadequate reference standard, extreme concerns regarding imprecision for one study *[15]* and very serious concerns regarding indirectness; none of the studies reported whether participants were asymptomatic, in one study *[17]* criteria for the diagnosis of clinically significant disease likely differed from that used in current practice, and three of the four studies *[15][17][18]* used a PSA threshold higher than the currently recommended threshold of 3.0 µg/L.

Values and preferences

No substantial variability expected

Most individuals would consider the detection of clinically significant disease more important than the risk of unnecessary referrals for further investigations.

Resources and other considerations

Important negative issues

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

Not all individuals undergoing testing for early detection of prostate cancer in the Australian primary care setting would be comfortable undergoing a DRE. There is evidence from a single US study to suggest that performing a DRE may be a barrier to/ disincentive for testing for the early detection of prostate cancer *[12]*.

Feasibility

There is variation in the confidence of primary care physicians in Australia in performing a DRE to detect possible prostate cancer. In a recent Australian survey of doctors in training in general practice 46.8% (n = 22) were comfortable in performing a DRE *[47]*.

Rationale

The balance of the benefits and harms of DRE in addition to PSA testing for the early detection of clinically significant prostate cancer in the Australian primary care setting is unclear. There is evidence to suggest that DRE may be a disincentive to individuals considering testing for the early detection of prostate cancer. Taken together, DRE is not recommended in this setting.

No areas of major debate about the evidence and the recommendations were identified. Recommendations were reached with full consensus.

Clinical question/ PICO

Population: Individuals at risk of prostate cancer without a history of prostate cancer or symptoms that might indicate prostate cancer
Intervention: PSA and DRE tests
Comparator: PSA test only

Summary

Four studies *[15][16][17][18]* were identified that examined the benefits and harms of using DRE in addition to total PSA levels as initial tests to identify individuals likely to have clinically significant prostate cancer (ISUP ≥ 2).

The addition of DRE to PSA testing increased prostate cancer detection at the expense of an increase in the number of unnecessary referrals for further investigation. How many additional unnecessary referrals for further investigation that would occur for each additional clinically significant cancer detected, depends on the underlying prevalence of clinically significant prostate cancer as well as the diagnostic accuracy of DRE. These could not be determined in three of the studies evaluated *[15][16][18]* because only those individuals who tested positive underwent biopsy, rendering the results of these studies difficult to interpret and apply to the clinical question.

In the fourth study *[17]* all individuals regardless of their PSA test results underwent biopsy enabling the calculation of sensitivity and specificity and the calculation of the number of additional unnecessary referrals for further investigation (harms) per additional clinically significant prostate cancer detected (benefit) for a specific prevalence of clinically important prostate cancer. Based on the results of this study, if the prevalence of clinically significant prostate cancer is

- 5% - the number of unnecessary referrals for further investigation with the addition of DRE to PSA testing using a threshold of 4.0 µg/L would be 11.0, and
- 10% - the number of unnecessary referrals for further investigation with the addition of DRE to PSA testing using a threshold of 4.0 µg/L would be 4.9.

However, it is important to note that there is considerable uncertainty surrounding the applicability of this data to the current clinical context for the following reasons:

- Criteria for the diagnosis of clinically significant disease is likely to be different to that used in current practice as the study was commenced prior to 2005 when the Gleason score categories were defined differently.
- Current clinical practice in Australia uses a threshold PSA level of 3.0 µg/L as the trigger point for further clinical investigations.
- The study did not report whether participants were asymptomatic
- Sextant biopsies were recommended.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** PSA test only	**Intervention** PSA and DRE tests	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant prostate cancer detected where the prevalence of clinically significant disease is 5%. 8 Critical	Based on data from 5,101 participants in 1 studies.	DRE in addition to PSA testing using a PSA threshold of 4.0µg/L is estimated to increase the number of clinically significant cancers detected in a population of 1000 asymptomatic individuals by 7 (95%CI: 3, 13), based on a relative sensitivity of 1.38 (95% CI: 1.14,1.68).		**Very low** 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 µg/L and the Gleason scores were highly likely to have been determined prior to 2005 when criteria for Gleason scores were revised.	If DRE is added to PSA testing in the primary care setting, we are uncertain whether the increases in clinically significant prostate cancer are unimportant for asymptomatic individuals if a PSA threshold of 3.0 µg/L is used.
Unnecessary further	Based on data from 5,101 participants in 1 studies.	DRE in addition to PSA testing using a PSA threshold of 4.0 µg/L is estimated to		**Very low** Serious concerns re bias due to	If DRE is added to PSA testing in the primary care setting, we are uncertain

Outcome Timeframe	**Study results and measurements**	**Comparator** PSA test only	**Intervention** PSA and DRE tests	**Certainty of the evidence** (Quality of evidence)	**Summary**
investigations where the prevalence of clinically significant disease is 5%. 7 Critical		increase the number of unnecessary further investigations in a population of 1000 asymptomatic individuals by 77 (95%CI: 69, 95) based on a relative specificity of 0.91 (95% CI: 0.89, 0.92).		inadequate reference standard and very serious concerns re indirectness as results were reported for a PSA threshold of 4.0 not 3.0 µg/L and the Gleason scores were highly likely to have been determined prior to 2005 when criteria for Gleason scores were revised.	whether the increases in unnecessary further investigations are clinically unimportant for asymptomatic individuals if a PSA threshold of 3.0 µg/L is used.
Number of additional unnecessary further investigations to detect an additional clinically significant cancer where the prevalence of clinically significant disease is 5% or 10%. 7 Critical	Based on data from 5,101 participants in 1 studies.	DRE in addition to PSA testing with a threshold of 4.0 µg/L is estimated to result in: • 11.0 additional further investigations per additional clinically significant prostate cancer detected in a population with a prevalence of clinically significant prostate cancer of 5% • 4.9 additional further investigations per additional clinically significant prostate cancer detected in a population with a prevalence of clinically significant prostate cancer of 10%		**Very low** 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 µg/L and the Gleason scores were highly likely to have been determined prior to 2005 when criteria for Gleason scores were revised.	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 3.0 µg/L and the prevalence of clinically significant disease is 5% or 10%.
Number of additional unnecessary further investigations to detect an additional clinically significant cancer for individuals with PSA < 3.0µg/L where the prevalence of clinically significant disease is unknown.	Based on data from 4 participants in 1 studies.	DRE in addition to PSA testing with a threshold of 3.0 µg/L is estimated to result in 80.0 (95%CI: 4.9, 1,301.3) additional further investigations per additional clinically significant prostate cancer detected.		**Very low** 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.	The number of additional unnecessary 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 PSA threshold of 3.0 µg/L.

Outcome Timeframe	**Study results and measurements**	**Comparator** PSA test only	**Intervention** PSA and DRE tests	**Certainty of the evidence** (Quality of evidence)	**Summary**
7 Critical					
Number of additional unnecessary further investigations to detect an additional clinically significant cancer for individuals with PSA < 4.0µg/L where the prevalence of clinically significant disease is unknown. 7 Critical	Based on data from 567 participants in 3 studies.	DRE in addition to PSA testing with a threshold of 4.0 µg/L is estimated to result in a 7.46 (95%CI: 2.08, 26.74) additional further investigations per additional clinically significant prostate cancer detected. The prevalence of clinically significant prostate cancer in the largest study was 4.7% and unknown for the other 2 studies.		**Very low** 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 µg/L, the study was undertaken in a tertiary setting not primary care setting and unclear whether participants symptomatic or asymptomatic.	The 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 PSA threshold of 3.0 µg/L.

References

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Good practice statement

4.2 Although DRE is not recommended as a routine test for men who, after advice, wish to be tested for the presence of prostate cancer, it will still be an important part of the man's assessment on referral to a urologist or other specialist for further assessment prior to consideration for biopsy.

Review by 2030, subject to emerging evidence

Rationale

This Good practice statement has been retained from the Prostate Cancer Foundation of Australia. 2016 Clinical Practice Guidelines for Prostate Specific Antigen (PSA) Testing and Early Management of Test-detected Prostate Cancer. 2016. Website

5. Primary health care setting - PSA testing

Prostate-specific antigen (PSA) is the first line test in the detection of clinically significant prostate cancer. It is a continuous parameter, with higher levels indicating greater likelihood of prostate cancer whilst some men may harbour clinically significant prostate cancer despite having low serum PSA. As described in the EAU Guidelines, PSA may also be elevated in benign prostate hyperplasia, prostatitis and other non-malignant conditions. The Guidelines state that interpretation of PSA levels in the context of early detection of prostate cancer must account for these factors, including:

- **Biological factors:**
  - *Biological variation*: PSA levels for an individual can fluctuate over time and may increase transiently following sexual activity *[360]*, *[361]*, *[377]*
  - *Urinary tract infection*: recent infection can elevate PSA levels *[362]*, *[363]*, *[378]*
  - *Acute urinary retention*: can cause an increase in serum PSA *[364]*, *[365]*
  - *Hypogonadism/low testosterone levels*: can be associated with lower PSA levels *[366]*
  - *Obesity:* serum PSA concentrations are reduced in the presence of obesity and when the testosterone concentration is low *[381]*
- **Medical procedures and medications:**
  - *Biopsy*: can cause transient increases in serum PSA *[367]*, *[368]*
  - *5-α reductase inhibitors*: used in management of benign prostatic hyperplasia and other conditions, can lower serum PSA levels by up to 50% *[369]*, *[370]*
  - *Oestrogens*: used in the management of medical conditions, and by transgender females *[371]*, *[372]*.
- **Measurement factors:**
  - *Inter-assay variation*: there are measurement variations between PSA assays *[373]*
  - *Sample preparation*: preparation and storage of samples can impact PSA measurement *[374]*, *[375]*.
- Digital rectal examination does not affect PSA levels *[376]*.

In cases of a moderately elevated PSA, a repeat test after a few weeks should be considered to confirm the indication for further diagnostic analysis, as one-third of men with a PSA <10 µg/L had a difference of greater than ±1.0 µg/L at the second measurement. Within 1-2 months PSA drops to below 3 µg/L in about one-fifth of males.

Clinical Questions

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? (Clinical question 5)*

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? (Clinical question 6)*

Background

There has been considerable change in thinking and practice for the early detection of prostate cancer since the 2016 Guidelines were published. The literature from long term PSA testing trials has matured demonstrating improved prostate cancer metastasis free and overall survival. There has been widespread clinical uptake of pre-biopsy triage with multiparametric MRI (mpMRI) and increased utilisation of active surveillance in Australian practice. Together, these have dramatically decreased the previously reported harm associated with the use of PSA alone as a testing strategy. To reflect these changes, development of these Guidelines focused on a risk-adapted, harm minimisation testing program for the early detection of prostate cancer in Australia, as opposed to a PSA testing paradigm which was the focus of the 2016 Guidelines.

A male's risk of developing clinically significant prostate cancer depends on multiple factors, known and unknown, resulting in a continuum of risk at any point in time and age. Currently, it is not possible to undertake a precise risk assessment. Instead in these Guidelines, risk is considered as either present or not based on age, family history and ethnicity.

Following the approaches used in recent international prostate cancer early detection guidelines *[9]*, *[342]*, males are considered to be at high or higher risk if they have a risk of clinically significant prostate cancer or prostate cancer death that is at least double that of the overall risk for the Australian male population.

In these Guidelines, for the purposes of deciding who and how to offer PSA testing, it has been assumed that males who know of any risk factors are considered to be at higher risk than those who do not know. For more information refer to Section A: Risk assessment and Section C: Priority populations.

Whilst PSA is an essential step in the early detection of prostate cancer, these Guidelines have transitioned from the role of PSA testing alone to the combination of PSA testing with mpMRI triage prior to selective targeted and systematic prostate biopsy to arrive at a diagnosis of prostate cancer.

Good practice statement

5.1 For males aged 50 years and over, initiate a discussion regarding the benefits and possible harms of testing for the early detection of prostate cancer.

For males aged 40 to 49 years, assess whether they are at higher risk* of prostate cancer than the general population.

For males aged 40 to 49 years who are assessed as not at higher risk but who enquire about their prostate health, it is reasonable to discuss the benefits and possible harms of the early detection of prostate cancer.

To be read in conjunction with recommendations 5.3, 5.4 and 5.5.

Refer Section B: Decision support for approaches to decision support.

*Males are considered to be at higher risk if they have a risk of clinically significant prostate cancer or prostate cancer death that is at least double that of the overall risk for the Australian male population. Higher risk includes, but is not restricted to, males with certain patterns of family history, Black males of sub-Saharan African ancestry and/or males with confirmed *BRCA2* gene mutations. For further details, refer to Section A: Risk assessment.

Review by 2030, subject to emerging evidence

Clinical question/ PICO

Population: Males with no history or symptoms of prostate cancer who are not at higher risk
Intervention: PSA testing with or without DRE
Comparator: No PSA testing

Summary

No trials were found that directly compared PSA testing strategies.

Three randomised controlled trials compared PSA testing protocols with usual care and reported long term (greater than 13 years) prostate cancer mortality outcomes and two reported cases of metastases. Effects were assessed as clinically important or not clinically important based on minimal clinically important differences (MCIDs) for prostate cancer mortality and metastases predetermined by a reference group consisting of a consumer, a general practitioner, a urology nurse practitioner and clinical specialists (the MCID Wording Group) following GRADE guidance provided by Schunemann 2022 *[305]*.

The decrease in prostate cancer mortality with PSA testing was not clinically important in two of the trials; the Cluster Randomized Trial of PSA testing for Prostate Cancer (CAP trial) in which men were offered a single PSA test *[246]* and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial) which had high rates of contamination in the control group *[271]*. In contrast there was a clinically important difference in prostate cancer mortality in The European Randomised Study of Screening for Prostate Cancer (ERSPC) for the combined results for the seven similar ERSPC PSA testing strategies based on regular PSA testing starting at ages 55-69 *[212]*. Similar results were reported for metastases at diagnosis or on progression. In the PLCO trial the decrease in metastatic cases with PSA testing was not clinically important at 15 years follow-up *[270]* whereas in the ERSPC trial (combined data from 4 centres) at 12 years there was a clinically important decrease in metastatic cases with testing *[300]* and this decrease continued to be clinically important with longer follow-up at the Rotterdam centre, the only ERSPC centre for which there were centre-specific results for metastases *[159]*.

Of the seven ERSPC PSA protocols for which results were available the largest decrease in prostate cancer at 14-18 years follow-up was seen for the protocol used at the Goteborg centre where men were offered PSA testing every 2 years using a PSA threshold of 2.5-3.4 µg/L starting at ages 50-64 and ceasing after age 69 *[209]*, *[210]*, *[212]*. The certainty of the evidence was high that the decrease using this protocol was clinically

important at 14-18 years follow-up. Decreases in prostate cancer mortality continued to be clinically important with longer follow-up for the Goteborg protocol *[183]*.

Results for metastases at diagnosis or on progression for the two trials reporting this outcome were similar to those for prostate cancer mortality. In the PLCO trial the decrease in metastatic cases with PSA testing was not clinically important at 15 years follow-up *[270]* whereas in the ERSPC trial (combined data from 4 centres) at 12 years there was a clinically important decrease in metastatic cases with testing *[300]* and this decrease continued to be clinically important with longer follow-up at the Rotterdam centre, the only ERSPC centre for which there were centre-specific results for metastases *[159]*.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths - Annual PSA testing using threshold of 4 µg/L for 6 years + annual DRE for 4 years starting at age 55-74 years 16 years 9 Critical	Relative risk 0.93 (CI 95% 0.81 — 1.08) Based on data from 76,683 participants in 1 studies.	**62** per 10.000 Difference:	**58** per 10.000 **4 fewer per 10.000** (CI 95% 12 fewer — 5 more)	**Low** Downgraded by two levels due to concerns re risk of bias and indirectness	In a population of asymptomatic men annual PSA testing using a threshold of 4 µg/L 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.
Prostate cancer-specific deaths – Single PSA test using threshold of 3 µg/L at ages 50-69 years 15 years 9 Critical	Relative risk 0.92 (CI 95% 0.85 — 0.99) Based on data from 415,357 participants in 1 studies.	**78** per 10.000 Difference:	**72** per 10.000 **6 fewer per 10.000** (CI 95% 12 fewer — 1 fewer)	**High**	In a population of asymptomatic men a single PSA test using a threshold of 3 µg/L at ages 50 to 69 results in a clinically unimportant decrease in prostate cancer mortality at 15 years when compared with usual care.
Prostate cancer-specific deaths – PSA testing using thresholds of primarily of 3-4 µg/L primarily every 4 years starting at ages 55-69 and ceasing primarily at age 74 16 years 9 Critical	Relative risk 0.8 (CI 95% 0.72 — 0.89) Based on data from 162,241 participants in 1 studies.	**89** per 10.000 Difference:	**71** per 10.000 **18 fewer per 10.000** (CI 95% 25 fewer — 10 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men PSA testing using a threshold of primarily 3 or 4 µg/L 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.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths – PSA testing using a threshold of 3-10 µg/L every 4-7 years starting at ages 55-69 and ceasing after 3 screens or age 74 16 years 9 Critical	Relative risk 0.79 (CI 95% 0.44 — 1.34) Based on data from 8,562 participants in 1 studies.	**89** per 10.000 Difference:	**70** per 10.000 **19 fewer per 10.000** (CI 95% 50 fewer — 30 more)	**Low** Downgraded by two levels due to very serious concerns re imprecision	In a population of asymptomatic men PSA testing using a threshold of 3-10 µg/L 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.
Prostate cancer-specific deaths – PSA testing using a threshold of 4 µg/L every 4 years (with triage test if PSA 3.0-3.9 µg/L) starting at ages 55, 59, 63 and 67 and ceasing after 3 screens or age 71 16 years 9 Critical	Relative risk 0.91 (CI 95% 0.77 — 1.06) Based on data from 80,379 participants in 1 studies.	**89** per 10.000 Difference:	**81** per 10.000 **8 fewer per 10.000** (CI 95% 20 fewer — 5 more)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men PSA testing using a threshold of 4 µg/L every 4 years (with triage test if PSA 3.0-3.9 µg/L) 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.
Prostate cancer-specific deaths – PSA testing using a threshold of 4 µg/L every 4 years (with triage test if PSA 2.5-3.9 µg/L) starting at ages 55-69 and ceasing after age 74 16 years 9 Critical	Relative risk 0.99 (CI 95% 0.66 — 1.49) Based on data from 14,515 participants in 1 studies.	**89** per 10.000 Difference:	**88** per 10.000 **1 fewer per 10.000** (CI 95% 30 fewer — 44 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision	In a population of asymptomatic men we are uncertain as to whether PSA testing using a threshold of 4 µg/L every 4 years (with triage test if PSA 2.5-3.9 µg/L) 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.
Prostate cancer-specific deaths – PSA testing using a threshold of 3-4 µg/L (triage if	Relative risk 0.67 (CI 95% 0.53 — 0.85) Based on data from 34,833 participants in 1 studies.	**89** per 10.000 Difference:	**60** per 10.000 **29 fewer per**	**Moderate** Downgraded by one level due to serious concerns re imprecision.	In a population of asymptomatic men PSA testing using a threshold of 3 or 4 µg/L every 4 years starting at ages 55-69 and

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
PSA 1.0-3.9 for 2 years) every 4 years starting at ages 55-69 and ceasing after age 74 16 years 9 Critical			**10.000** (CI 95% 42 fewer — 13 fewer)		ceasing after age 74 probably results in a clinically important (small) decrease in prostate cancer mortality at 16 years when compared with usual care.
Prostate cancer-specific deaths – PSA testing using a threshold of 3 µg/L every 4 years starting at ages 55-69 and ceasing after 3 screens or age 74 16 years 9 Critical	Relative risk 0.65 (CI 95% 0.13 — 2.63) Based on data from 2,197 participants in 1 studies.	**89** per 10.000 Difference:	**58** per 10.000 **31 fewer per 10.000** (CI 95% 77 fewer — 145 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision.	In a population of asymptomatic men, we are uncertain as to whether PSA testing using a threshold of 3 µg/L 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.
Prostate cancer-specific deaths – PSA testing using thresholds of 2.5-3.4 µg/L every 2 years starting at ages 55-64 and ceasing after age 69	Relative risk 0.63 (CI 95% 0.44 — 0.88) Based on data from 11,852 participants in 1 studies.	**89** per 10.000 Difference:	**56** per 10.000 **33 fewer per 10.000** (CI 95% 50 fewer — 11 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men, PSA testing using thresholds of 2.5-3.4 µg/L 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.
Prostate cancer-specific deaths – PSA testing using thresholds of 2.5-3.4 µg/L every 2 years starting at ages 50-64 and ceasing after age 69 14 years 9 Critical	Relative risk 0.56 (CI 95% 0.39 — 0.82) Based on data from 19,904 participants in 1 studies.	**90** per 10.000 Difference:	**50** per 10.000 **40 fewer per 10.000** (CI 95% 55 fewer — 16 fewer)	**High**	In a population of asymptomatic men, PSA testing using thresholds of 2.5-3.4 µg/L 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 years when compared with usual care.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths – PSA testing using thresholds of 2.5-3.4 µg/L every 2 years starting at ages 50-64 and ceasing after age 69 18 years 9 Critical	Relative risk 0.65 (CI 95% 0.49 — 0.87) Based on data from 19,899 participants in 1 studies.	**150** per 10.000 Difference:	**98** per 10.000 **52 fewer per 10.000** (CI 95% 76 fewer — 19 fewer)	**High**	In a population of asymptomatic men, PSA testing using thresholds of 2.5-3.4 µg/L 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 18 years when compared with usual care.
Prostate cancer-specific deaths – PSA testing using thresholds of 2.5-3.4 µg/L every 2 years starting at ages 50-64 and ceasing after age 69 22 years 9 Critical	Relative risk 0.71 (CI 95% 0.55 — 0.91) Based on data from 19,894 participants in 1 studies.	**213** per 10.000 Difference:	**151** per 10.000 **62 fewer per 10.000** (CI 95% 96 fewer — 19 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men, PSA testing using thresholds of 2.5-3.4 µg/L 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.
Prostate cancer-specific deaths – PSA testing using a threshold of 3-4 µg/L (triage if PSA 1.0-3.9 for 2 years) every 4 years starting at ages 55-69 and ceasing after age 74 21 years 9 Critical	Relative risk 0.73 (CI 95% 0.61 — 0.88) Based on data from 34,833 participants in 1 studies.	**159** per 10.000 Difference:	**116** per 10.000 **43 fewer per 10.000** (CI 95% 62 fewer — 19 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men, PSA testing using a threshold of 3 or 4 µg/L every 4 years starting at ages 55-69 and ceasing after age 74 probably results in a clinically important (moderate) decrease in prostate cancer mortality at 21 years when compared with usual care.
Metastases at diagnosis or on progression - Annual PSA testing using threshold of 4 µg/L for 6 years + annual DRE for 4	Relative risk 0.98 (CI 95% 0.81 — 1.18) Based on data from 76,683 participants in 1 studies.	**80** per 10.000 Difference:	**78** per 10.000 **2 fewer per 10.000** (CI 95% 15 fewer — 14 more)	**Low** Downgraded by two levels due to concerns re risk of bias and indirectness	In a population of asymptomatic men, annual PSA testing using a threshold of 4 µg/L 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

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
years starting at age 55-74 years 15 years 9 Critical					diagnosis or on progression at 15 years when compared with usual care.
Metastases at diagnosis or on progression - PSA testing using thresholds of primarily of 3-4 µg/L primarily every 4 years starting at ages 55-69 and ceasing primarily at age 74 12 years 9 Critical	Relative risk 0.7 (CI 95% 0.6 — 0.82) Based on data from 76,813 participants in 1 studies.	**104** per 10.000 Difference:	**73** per 10.000 **31 fewer per 10.000** (CI 95% 42 fewer — 19 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men, PSA testing using a threshold of primarily 3 or 4 µg/L 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.
Metastases at diagnosis or on progression - PSA testing using a threshold of 3-4 µg/L (triage if PSA 1.0-3.9 for 2 years) every 4 years starting at ages 55-69 and ceasing after age 74 21 years 9 Critical	Relative risk 0.67 (CI 95% 0.58 — 0.78)	**349** per 10.000 Difference:	**234** per 10.000 **115 fewer per 10.000** (CI 95% 147 fewer — 77 fewer)	**High**	In a population of asymptomatic men, PSA testing using a threshold of 3 or 4 µg/L every 4 years starting at ages 55-69 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.

Good practice statement

5.2 The early detection of clinically significant prostate cancer requires an individualised, risk-adapted, harm-minimisation approach which may include decision support, PSA testing and multiparametric magnetic resonance imaging (mpMRI) in conjunction with:

- Digital rectal examination (refer Digital rectal examination).
- Harm-minimisation strategies including prostate biopsy techniques (refer 6. Specialist setting- Multiparametric magnetic resonance imaging and 7. Specialist setting - Prostate biopsy).
- Management strategies including active surveillance (refer 8. Active surveillance).

This co-ordinated approach is consistent with a harm minimisation imperative and leads to a reduction in over-treatment..

Refer 5.1 Good practice statement

Refer 5.3 Strong recommendation

Review by 2030, subject to emerging evidence

Strong recommendation

5.3 We recommend offering males aged 50 to 69 years PSA testing every two years.

If total PSA is 3.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, offer referral for further investigation.

Refer 5.1 Good practice statement

Refer 5.2 Good practice statement.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

Benefits/desirable effects

Three RCTs compared PSA testing protocols with usual care and reported long term (> 13 years) prostate cancer mortality outcomes. All were undertaken in the pre-MRI era. Thresholds for the magnitude of the size of the benefits were based on minimal clinically important differences (MCIDs) for prostate cancer mortality and metastases predetermined by a reference group consisting of a consumer, a general practitioner, a urology nurse practitioner and clinical specialists (the MCID Working Group refer Appendix 1: Governance structure and group membership) following GRADE guidance provided by Schunemann 2022 *[305]*.

In the Cluster Randomized Trial of PSA testing for Prostate Cancer (CAP trial) a single PSA test using a threshold of 3 µg/L for men aged 50 to 69 years resulted in a clinically unimportant decrease in prostate cancer mortality at 15 years when compared with usual care *[246]*.

In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial) annual PSA testing using a threshold of 4 µg/L for 6 years starting at ages 55 to 74 plus annual DRE for the first 4 years resulted in a clinically unimportant difference in prostate cancer mortality at 16 years when compared with usual care *[271]*.

In contrast, in The European Randomised Study of Screening for Prostate Cancer (ERSPC) which combined results from seven similar PSA testing strategies, PSA testing using a PSA threshold of primarily 3 or 4 µg/L primarily every 4 years starting at ages 55-69 and ceasing primarily after age 74 resulted in a clinically important (small) decrease in prostate cancer mortality at 16 years when compared with usual care *[212]*. Of the six ERSPC centres with 14-18 years follow-up, the greatest decrease in prostate cancer mortality, was seen with protocol used at the Goteborg centre. At the Goteborg centre PSA testing was offered every 2 years using a PSA threshold of 2.5-3.4 µg/L starting at ages 50-64 and ceasing after age 69 *[209]*, *[210]*. Based on minimal clinically important differences (MCIDs) of 14 or 18 deaths per 10,000 for 14- and 18-year follow-up respectively, and thresholds for moderate differences of double the MCID and thresholds for large differences of four times the MCID these were clinically important moderate differences. Clinically important (moderate) decreases in prostate cancer mortality continued to be seen at 22 years using this

protocol *[183]* and also at 21 years with PSA testing using a threshold of 3 or 4 µg/L every 4 years starting at ages 55-69 and ceasing after age 74 *[159]*. The decreases in prostate cancer mortality at 21-22 years were driven by the higher risks of prostate cancer mortality in the control groups as they age; at 21-22 years the relative risk estimates had started to reverse back towards 1.00 as the effects of screening decline post screening.

The outcome, metastases at diagnosis or on progression, was reported for the PLCO at 15 years, the ERSPC (combined results from 4 centres) at 12 years and the Netherlands ERSPC centre at 21 years. The results were similar to those for prostate cancer mortality. In the PLCO trial annual PSA testing using a threshold of 4 µg/L for 6 years starting at ages 55 to 74 plus annual DRE for the first 4 years resulted in a clinically unimportant difference in metastases cases at 15 years when compared with usual care *[270]*.

In contrast in the ERSPC (combined results from 4 centres), PSA testing using a PSA threshold of primarily 3 or 4 µg/L primarily every 4 years starting at ages 55-69 and ceasing primarily after age 74 resulted in a clinically important (small) decrease in metastases cases at 12 years when compared with usual care *[300]*. At 21 years there was a clinically important (moderate) decrease in metastases cases with PSA testing using a threshold of 3 or 4 µg/L every 4 years starting at ages 55-69 and ceasing after age 74 at the ERSPC Rotterdam centre *[159]*. No effect estimates for metastases were found for the other ERSPC protocols.

Harms/ undesirable effects

The potential harms of PSA testing in the pre-MRI era are well established for men with average risk disease. Clinical trials such as the European Randomised Study of Screening for Prostate Cancer (ERSPC) *[209]*, *[121]* and modelling studies *[195]* have shown that PSA testing has led to increased numbers of diagnoses, particularly of low-risk cancers, and biopsies. However, it is critical to note that these studies were undertaken in the pre-MRI era and none of the included trials provided evidence of harms in the era of multiparametric MRI and widespread uptake of active surveillance. Using multiparametric MRI to triage men with an elevated PSA level for biopsy as recommended in these Guidelines will reduce the number of unnecessary biopsies by approximately 50% and thereby will reduce the detection of low-risk disease by between 32-64% (See Specialist setting - Multiparametric magnetic resonance imaging). In Australia, where multiparametric MRI is already standard of care to triage men to biopsy, there were 52,080 diagnostic MRI scans funded in 2024 for the investigation of an elevated PSA > 3.0 µg/L *[307]*.

Offering active surveillance to men with lower risk prostate cancer as recommended in these Guidelines will reduce the number of men at risk of the long-term side effects of definitive treatments. In Australia and New Zealand active surveillance is now well accepted as the first line of treatment for low-risk disease. 80% of patients diagnosed with low-risk disease in 2021 were managed with active surveillance, having increased from 66% in 2015 *[263]*.

As there was no randomised evidence for harms in the context of multiparametric triage to biopsy and widespread uptake of active surveillance, the magnitude of the harms in this context could not be estimated using MCIDs and instead was estimated by the Working Group to be small.

Balance of benefits and harms/ desirable and undesirable effects

It should be noted that the magnitude of harms are estimates only based on expert and consumer opinion whereas the magnitude of benefits are based on reported evidence and are most likely underestimates. Any likely contamination in the control arm will reduce the effect estimates. These trials primarily used what are now considered inadequate sextant biopsies. Furthermore, pre-biopsy MRI facilitates more precise target biopsies and biopsy triage, resulting in the higher detection rate clinically significant cancers and a lower detection rate of clinically insignificant cancers *[163]*.

In the context of Australian practice in which multiparametric MRI triage is used, the great majority of men with low-risk disease are managed with active surveillance and the management and prevention of treatment related morbidity has improved, the risks and harms of PSA testing in Australia have been substantially reduced. In the absence of any direct evidence of harms in this context, the reported clinically important moderate decreases in prostate cancer mortality seen at 14 or more years follow-up when using the Goteborg trial protocol and metastatic disease at 21 years follow-up when using the ERSPC Rotterdam protocol would outweigh any estimated small harms associated with PSA testing for the early detection of prostate cancer for men not at higher risk.

Certainty of the evidence

High

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 GRADE guidance *[302]*, *[305]*.

As per the GRADE evidence to decision making process, the certainty of the evidence for each specific PSA testing protocol and study was important in the working group's decision making when taking the respective clinical effect of each protocol and study into account.

The certainty of the evidence was low for the PLCO protocol having a clinically unimportant effect due to high risk of contamination in the control group and serious concerns re indirectness, as the results were not directly relevant to an unscreened population and it is likely that a substantial proportion of participants had received PSA test in 3 years prior to enrolment.

In contrast, the certainty of the evidence was high for a single PSA test resulting in clinically insignificant decrease in prostate cancer mortality.

For men aged 55-69 at the start of screening the certainty of the evidence as to whether the effects for prostate cancer mortality were clinically important ranged from very low to moderate for the different ERSPC protocols for men due to varying degrees of concern regarding imprecision.

In contrast, for the protocol in which men started screening at ages 50-64 which resulted in the greatest decrease in prostate cancer mortality i.e. PSA testing with PSA thresholds of 2.5-3.4 µg/L every 2 years starting at ages 50-64 and ceasing after age 69 the certainty of the evidence that the effect was clinically important was high at 14- and 18-years follow-up (but only moderate at 22 years follow-up).

The certainty of the evidence for a clinically significant decrease in metastases at diagnosis or on progression was moderate due to concerns regarding imprecision for the ERSPC (4 centres) at 12 years and high for the Netherlands ERSPC centre at 21 years.

Values and preferences

No substantial variability expected

A systematic review *[335]* found substantial variability as to how men valued a long-term reduction in risk of prostate cancer mortality versus an increased risk of unnecessary biopsies and treatment. This evidence came from studies undertaken prior to the introduction of multiparametric MRI triage prior to biopsy, and before active surveillance had become a routine management option for men with low-risk localised disease. This evidence is not reflective of contemporary practice in Australia. In the era of multiparametric MRI triage, active surveillance, focal therapy and improved management and prevention of treatment related morbidity the risks and potential harms of PSA testing have been reduced. In this era professional experience and consumer input point to most men not at higher risk of prostate cancer mortality preferring PSA testing, having regard to the long-term reduction in risk of prostate cancer mortality, reduction in risk of living with metastatic prostate cancer that may include treatment with androgen deprivation therapy (possible side effects-reduced libido and sexual function, fatigue, depression, hot flashes, increased risk of diabetes and its complications, and osteoporosis and fracture, and increased risk of cardiovascular disease), the reduced likelihood of requiring a biopsy and the reduced likelihood of undergoing unnecessary treatment of low risk disease. The high acceptance rate of active surveillance in Australia and New Zealand (80% of patients diagnosed with low-risk disease in 2021 managed with active surveillance *[263]*) demonstrates that men are more comfortable living with this approach to managing low risk prostate cancer.

Males and their families place a higher value on an early diagnosis of prostate cancer compared to the morbidity of metastatic disease and premature death. They prefer to be able to make an informed decision of the management options of their prostate cancer having been diagnosed earlier and whilst curable.

Overwhelming clinical experience in the era of multiparametric MRI and longer-term active surveillance follow up demonstrating safety and efficacy indicates that there is minimal variability in men's acceptance of the PSA test once they have been informed of the benefits and potential harms.

Resources and other considerations

No important issues with the recommended alternative

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

PSA testing using a PSA threshold of 3.0 µg/L every 2 years from age 50 until age 69 would likely be acceptable to men, their caregivers and health providers. This PSA testing protocol has not changed from that previously recommended in 2016 and continues to be used in Australian practice.

Feasibility

PSA testing using a PSA threshold of 3.0 µg/L every 2 years from age 50 until age 69 is unlikely to be burdensome to men or the healthcare system. This PSA testing protocol has not changed from that previously recommended in 2016 and continues to be used in Australian practice.

Rationale

For PSA testing recommendations related to males who are not considered at higher risk of prostate cancer mortality, three studies were found that compared PSA testing protocols with usual care protocols. These studies reported long term (> 13 years) prostate cancer mortality outcomes and were all undertaken in the pre-mpMRI era. The first, the Cluster Randomized Trial of PSA testing for Prostate Cancer (CAP trial), showed that single PSA test did not result in a clinically important decrease in prostate cancer *[246]*. The second, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial), had high levels of contamination in the control group and was unable to show any benefits with PSA testing *[271]*.

The third, the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial, combined the results from several centres using different PSA testing protocols and showed with moderate certainty that regular PSA testing starting at ages 55-69 results in a clinically important decrease in prostate cancer mortality at 16 years when compared with usual care *[212]*. Of the ERSPC protocols, the decrease in prostate cancer was greatest and the certainty of the evidence high for the protocol used at the Goteborg centre, PSA testing every 2 years using a PSA threshold of 2.5-3.4 µg/L starting at ages 50-64 and ceasing after age 69 *[212]*, *[209]*, *[210]*. Based on pre-determined thresholds for small, moderate and large absolute effects the benefits of PSA testing using this protocol are moderate. This may be an underestimate as there was likely some contamination in the control arm and sextant biopsies were used, which are now known to be inadequate. In contrast, there is no evidence as to the magnitude of harms of PSA testing in an era of harm minimisation in which multiparametric MRI triage is used, reducing unnecessary biopsies by around 50%, active surveillance is the main management option for men diagnosed with low-risk prostate cancer and there is improved management and prevention of treatment related morbidity. In the absence of any relevant evidence the harms were estimated to be small in this context.

Overall, the evidence suggests that the benefits of PSA testing of men not at higher risk of prostate cancer mortality using a protocol similar to that used in the Goteborg trial outweigh any possible harms, particularly in the context of current Australian practice where multiparametric MRI is used to triage to biopsy and most men with low-risk disease are managed with active surveillance.

There was unanimous agreement around the direction of evidence. There was discussion around the strength of the evidence with 14 of 15 Working Group members supporting a Strong recommendation. Following further discussion, there was unanimous support for a Strong recommendation at the Working Group, EAP and PSC levels.

Clinical question/ PICO

Population: Males with no history or symptoms of prostate cancer who are not at higher risk
Intervention: PSA testing with or without DRE
Comparator: No PSA testing

Summary

No trials were found that directly compared PSA testing strategies.

Three randomised controlled trials compared PSA testing protocols with usual care and reported long term (greater than 13 years) prostate cancer mortality outcomes and two reported cases of metastases. Effects were assessed as clinically important or not clinically important based on minimal clinically important differences (MCIDs) for prostate cancer mortality and metastases predetermined by a reference group consisting of a consumer, a general practitioner, a urology nurse practitioner and clinical specialists (the MCID Wording Group) following GRADE guidance provided by Schunemann 2022 *[305]*.

The decrease in prostate cancer mortality with PSA testing was not clinically important in two of the trials; the Cluster Randomized Trial of PSA testing for Prostate Cancer (CAP trial) in which men were offered a single PSA test *[246]* and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial) which had high rates of contamination in the control group *[271]*. In contrast there was a clinically important difference in prostate cancer mortality in The European Randomised Study of Screening for Prostate Cancer (ERSPC) for the combined results for the seven similar ERSPC PSA testing strategies based on regular PSA testing starting at ages 55-69 *[212]*. Similar results were reported for metastases at diagnosis or on progression. In the PLCO trial the decrease in metastatic cases with PSA testing was not clinically important at 15 years follow-up *[270]* whereas in the ERSPC trial (combined data from 4 centres) at 12 years there was a clinically important decrease in metastatic cases with testing *[300]* and this decrease continued to be clinically important with longer follow-up at the Rotterdam centre, the only ERSPC centre for which there were centre-specific results for metastases *[159]*.

Of the seven ERSPC PSA protocols for which results were available the largest decrease in prostate cancer at 14-18 years follow-up was seen for the protocol used at the Goteborg centre where men were offered PSA testing every 2 years using a PSA threshold of 2.5-3.4 µg/L starting at ages 50-64 and ceasing after age 69 *[209]*, *[210]*, *[212]*. The certainty of the evidence was high that the decrease using this protocol was clinically important at 14-18 years follow-up. Decreases in prostate cancer mortality continued to be clinically important with longer follow-up for the Goteborg protocol *[183]*.

Results for metastases at diagnosis or on progression for the two trials reporting this outcome were similar to those for prostate cancer mortality. In the PLCO trial the decrease in metastatic cases with PSA testing was not clinically important at 15 years follow-up *[270]* whereas in the ERSPC trial (combined data from 4 centres) at 12 years there was a clinically important decrease in metastatic cases with testing *[300]* and this decrease continued to be clinically important with longer follow-up at the Rotterdam centre, the only ERSPC centre for which there were centre-specific results for metastases *[159]*.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths - Annual PSA testing using threshold of 4 µg/L for 6 years + annual DRE for 4 years starting at age 55-74 years 16 years 9 Critical	Relative risk 0.93 (CI 95% 0.81 — 1.08) Based on data from 76,683 participants in 1 studies.	**62** per 10.000 Difference:	**58** per 10.000 **4 fewer per 10.000** (CI 95% 12 fewer — 5 more)	**Low** Downgraded by two levels due to concerns re risk of bias and indirectness	In a population of asymptomatic men annual PSA testing using a threshold of 4 µg/L 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.
Prostate cancer-specific deaths – Single PSA test using threshold of 3 µg/L at ages 50-69 years 15 years 9 Critical	Relative risk 0.92 (CI 95% 0.85 — 0.99) Based on data from 415,357 participants in 1 studies.	**78** per 10.000 Difference:	**72** per 10.000 **6 fewer per 10.000** (CI 95% 12 fewer — 1 fewer)	**High**	In a population of asymptomatic men a single PSA test using a threshold of 3 µg/L at ages 50 to 69 results in a clinically unimportant decrease in prostate cancer mortality at 15 years when compared with usual care.
Prostate cancer-specific deaths – PSA testing using thresholds of primarily of 3-4 µg/L primarily every 4 years starting at ages 55-69 and ceasing primarily at age 74 16 years 9 Critical	Relative risk 0.8 (CI 95% 0.72 — 0.89) Based on data from 162,241 participants in 1 studies.	**89** per 10.000 Difference:	**71** per 10.000 **18 fewer per 10.000** (CI 95% 25 fewer — 10 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men PSA testing using a threshold of primarily 3 or 4 µg/L 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.
Prostate cancer-	Relative risk 0.79 (CI 95% 0.44 — 1.34)	**89**	**70**	**Low** Downgraded by	In a population of asymptomatic men PSA

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
specific deaths – PSA testing using a threshold of 3-10 µg/L every 4-7 years starting at ages 55-69 and ceasing after 3 screens or age 74 16 years 9 Critical	Based on data from 8,562 participants in 1 studies.	per 10.000 Difference:	per 10.000 **19 fewer per 10.000** (CI 95% 50 fewer — 30 more)	two levels due to very serious concerns re imprecision	testing using a threshold of 3-10 µg/L 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.
Prostate cancer-specific deaths – PSA testing using a threshold of 4 µg/L every 4 years (with triage test if PSA 3.0-3.9 µg/L) starting at ages 55, 59, 63 and 67 and ceasing after 3 screens or age 71 16 years 9 Critical	Relative risk 0.91 (CI 95% 0.77 — 1.06) Based on data from 80,379 participants in 1 studies.	89 per 10.000 Difference:	81 per 10.000 **8 fewer per 10.000** (CI 95% 20 fewer — 5 more)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men PSA testing using a threshold of 4 µg/L every 4 years (with triage test if PSA 3.0-3.9 µg/L) 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.
Prostate cancer-specific deaths – PSA testing using a threshold of 4 µg/L every 4 years (with triage test if PSA 2.5-3.9 µg/L) starting at ages 55-69 and ceasing after age 74 16 years 9 Critical	Relative risk 0.99 (CI 95% 0.66 — 1.49) Based on data from 14,515 participants in 1 studies.	89 per 10.000 Difference:	88 per 10.000 **1 fewer per 10.000** (CI 95% 30 fewer — 44 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision	In a population of asymptomatic men we are uncertain as to whether PSA testing using a threshold of 4 µg/L every 4 years (with triage test if PSA 2.5-3.9 µg/L) 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.
Prostate cancer-specific deaths – PSA testing using a threshold of 3-4 µg/L (triage if PSA 1.0-3.9 for 2	Relative risk 0.67 (CI 95% 0.53 — 0.85) Based on data from 34,833 participants in 1 studies.	89 per 10.000 Difference:	60 per 10.000 **29 fewer per 10.000** (CI 95% 42 fewer	**Moderate** Downgraded by one level due to serious concerns re imprecision.	In a population of asymptomatic men PSA testing using a threshold of 3 or 4 µg/L every 4 years starting at ages 55-69 and ceasing after age 74

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
years) every 4 years starting at ages 55-69 and ceasing after age 74 16 years 9 Critical			— 13 fewer)		probably results in a clinically important (small) decrease in prostate cancer mortality at 16 years when compared with usual care.
Prostate cancer-specific deaths – PSA testing using a threshold of 3 µg/L every 4 years starting at ages 55-69 and ceasing after 3 screens or age 74 16 years 9 Critical	Relative risk 0.65 (CI 95% 0.13 — 2.63) Based on data from 2,197 participants in 1 studies.	**89** per 10.000 Difference:	**58** per 10.000 **31 fewer per 10.000** (CI 95% 77 fewer — 145 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision.	In a population of asymptomatic men, we are uncertain as to whether PSA testing using a threshold of 3 µg/L 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.
Prostate cancer-specific deaths – PSA testing using thresholds of 2.5-3.4 µg/L every 2 years starting at ages 55-64 and ceasing after age 69	Relative risk 0.63 (CI 95% 0.44 — 0.88) Based on data from 11,852 participants in 1 studies.	**89** per 10.000 Difference:	**56** per 10.000 **33 fewer per 10.000** (CI 95% 50 fewer — 11 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men, PSA testing using thresholds of 2.5-3.4 µg/L 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.
Prostate cancer-specific deaths – PSA testing using thresholds of 2.5-3.4 µg/L every 2 years starting at ages 50-64 and ceasing after age 69 14 years 9 Critical	Relative risk 0.56 (CI 95% 0.39 — 0.82) Based on data from 19,904 participants in 1 studies.	**90** per 10.000 Difference:	**50** per 10.000 **40 fewer per 10.000** (CI 95% 55 fewer — 16 fewer)	**High**	In a population of asymptomatic men, PSA testing using thresholds of 2.5-3.4 µg/L 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 years when compared with usual care.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths – PSA testing using thresholds of 2.5-3.4 µg/L every 2 years starting at ages 50-64 and ceasing after age 69 18 years 9 Critical	Relative risk 0.65 (CI 95% 0.49 — 0.87) Based on data from 19,899 participants in 1 studies.	**150** per 10.000 Difference:	**98** per 10.000 **52 fewer per 10.000** (CI 95% 76 fewer — 19 fewer)	**High**	In a population of asymptomatic men, PSA testing using thresholds of 2.5-3.4 µg/L 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 18 years when compared with usual care.
Prostate cancer-specific deaths – PSA testing using thresholds of 2.5-3.4 µg/L every 2 years starting at ages 50-64 and ceasing after age 69 22 years 9 Critical	Relative risk 0.71 (CI 95% 0.55 — 0.91) Based on data from 19,894 participants in 1 studies.	**213** per 10.000 Difference:	**151** per 10.000 **62 fewer per 10.000** (CI 95% 96 fewer — 19 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men, PSA testing using thresholds of 2.5-3.4 µg/L 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.
Prostate cancer-specific deaths – PSA testing using a threshold of 3-4 µg/L (triage if PSA 1.0-3.9 for 2 years) every 4 years starting at ages 55-69 and ceasing after age 74 21 years 9 Critical	Relative risk 0.73 (CI 95% 0.61 — 0.88) Based on data from 34,833 participants in 1 studies.	**159** per 10.000 Difference:	**116** per 10.000 **43 fewer per 10.000** (CI 95% 62 fewer — 19 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men, PSA testing using a threshold of 3 or 4 µg/L every 4 years starting at ages 55-69 and ceasing after age 74 probably results in a clinically important (moderate) decrease in prostate cancer mortality at 21 years when compared with usual care.
Metastases at diagnosis or on progression - Annual PSA testing using threshold of 4 µg/L for 6 years + annual DRE for 4	Relative risk 0.98 (CI 95% 0.81 — 1.18) Based on data from 76,683 participants in 1 studies.	**80** per 10.000 Difference:	**78** per 10.000 **2 fewer per 10.000** (CI 95% 15 fewer — 14 more)	**Low** Downgraded by two levels due to concerns re risk of bias and indirectness	In a population of asymptomatic men, annual PSA testing using a threshold of 4 µg/L 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

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** PSA testing with or without DRE	**Certainty of the evidence** (Quality of evidence)	**Summary**
years starting at age 55-74 years 15 years 9 Critical					diagnosis or on progression at 15 years when compared with usual care.
Metastases at diagnosis or on progression - PSA testing using thresholds of primarily of 3-4 µg/L primarily every 4 years starting at ages 55-69 and ceasing primarily at age 74 12 years 9 Critical	Relative risk 0.7 (CI 95% 0.6 — 0.82) Based on data from 76,813 participants in 1 studies.	**104** per 10.000 Difference:	**73** per 10.000 **31 fewer per 10.000** (CI 95% 42 fewer — 19 fewer)	**Moderate** Downgraded by one level due to serious concerns re imprecision	In a population of asymptomatic men, PSA testing using a threshold of primarily 3 or 4 µg/L 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.
Metastases at diagnosis or on progression - PSA testing using a threshold of 3-4 µg/L (triage if PSA 1.0-3.9 for 2 years) every 4 years starting at ages 55-69 and ceasing after age 74 21 years 9 Critical	Relative risk 0.67 (CI 95% 0.58 — 0.78)	**349** per 10.000 Difference:	**234** per 10.000 **115 fewer per 10.000** (CI 95% 147 fewer — 77 fewer)	**High**	In a population of asymptomatic men, PSA testing using a threshold of 3 or 4 µg/L every 4 years starting at ages 55-69 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.

Strong recommendation

5.4 We recommend offering PSA testing to males who are at higher risk* and refer readers to refer 5.5 Consensus recommendation for testing regimen.

* Males are considered to be at higher risk if they have a risk of clinically significant prostate cancer or prostate cancer death that is at least double that of the overall risk for the Australian male population. Higher risk includes, but is not restricted to, males with certain patterns of family history, Black males of sub-Saharan African ancestry and/or males with confirmed *BRCA2* gene mutations.

For further details, refer to Section A: Risk assessment

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

Benefits/desirable effects

A single small (n = 4833) subgroup analysis of those with a family history (first degree relative) of prostate cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) reported a moderate decrease in prostate cancer mortality at 11 years with annual PSA testing for 6 years plus annual DRE for the first 4 years starting at ages 55-74 years *[236]*. No evidence was found for any other screening protocols for high-risk male populations.

Harms/undesirable effects

The potential harms of PSA testing are well established for men with average risk disease. Clinical trials such as the European Randomised Study of Screening for Prostate Cancer (ERSPC) *[209]*, *[121]* and modelling studies *[195]* have shown that PSA testing leads to increased numbers of diagnoses, particularly of low-risk cancers and increased numbers of biopsies. Using multiparametric MRI to triage men with an elevated PSA level to biopsy as recommended in these Guidelines will reduce the number of unnecessary biopsies by approximately 50% and thereby reduce the detection of low-risk disease between 32-64% (see Specialist setting - Multiparametric magnetic resonance imaging). Offering active surveillance to men with lower risk prostate cancer as recommended in these Guidelines will reduce the number of men at risk of the long-term side effects of definitive treatments.

We are not aware of any evidence as to the magnitude of these harms for men at higher risk of prostate cancer mortality or clinically significant disease.

Balance of benefits and harms/desirable and undesirable effects

In the context of multiparametric MRI triage, active surveillance for men with lower risk localised disease, focal therapy and the improved management and prevention of treatment related morbidity which have substantially reduced the risks and harms of PSA testing in Australia, the moderate decrease in prostate cancer mortality would likely outweigh the potential harms associated with PSA testing for prostate cancer for higher risk men.

The evidence supports testing for prostate cancer for men with a first degree relative who has been diagnosed with prostate cancer. However, the protocol used in this single study was designed to reduce prostate cancer mortality in a general screening population rather than a population at higher risk of aggressive disease and prostate cancer mortality.

In the absence of evidence in higher risk populations for protocols specifically designed for higher risk men or any other protocols it is not possible to make evidence-based recommendations as to the optimal PSA testing protocol to use for higher risk men.

Certainty of the evidence

Moderate

The overall certainty of the evidence as to the whether the decrease in prostate cancer mortality with PSA testing for higher risk men was clinically important was rated moderate due to imprecision. The high risk of contamination in the control group and the high levels of PSA testing prior to the trial would likely lead to underestimates of the actual effect of PSA testing in this trial and were not considered serious concerns.

Values and preferences

No substantial variability expected

A systematic review found substantial variability as to how men valued a long-term reduction in risk of prostate cancer mortality and increased risk of unnecessary biopsies and treatment *[335]*. This evidence came from studies undertaken prior to the introduction of multiparametric MRI triage for biopsy and before active surveillance had become a routine management option for men with low-risk localised disease. This evidence is not reflective of contemporary practice in Australia. In the era of mpMRI triage, active surveillance, focal therapy and improved management and prevention of treatment related morbidity the risks and potential harms of PSA testing have been reduced. In this era, professional experience and consumer input point to most men at higher risk of prostate cancer mortality preferring PSA testing having regard to the long-term reduction in risk of prostate cancer mortality, reduction in risk of living with the syndrome of metastatic prostate cancer that may include treatment with androgen deprivation therapy (possible side effects-reduced libido and sexual function, fatigue, depression, hot flashes, increased risk of diabetes and its complications, and osteoporosis and fracture, and increased risk of cardiovascular disease), the reduced likelihood of requiring a biopsy and the reduced likelihood of undergoing unnecessary treatment of low risk disease. The high acceptance rates of active surveillance in Australia demonstrates that men are more comfortable living with untreated low risk cancer *[263]*. Males and their families place a higher value on an early diagnosis of prostate cancer compared to the morbidity of metastatic disease and premature death. They prefer to be able to make an informed decision of the management options of their prostate cancer having been diagnosed earlier and whilst curable..

Overwhelming clinical experience in the era of MRI and longer term active surveillance follow up demonstrating safety and efficacy is that there is minimal variability in men's acceptance of the PSA test once they have been informed of the benefits and potential harms. Furthermore, men with a family history of prostate cancer when compared to those men without a family history are much more likely to seek testing having watched a loved one battle with living with metastatic prostate cancer and at times die from prostate cancer.

Resources and other considerations

No important issues with the recommended alternative

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

Offering PSA testing to men at higher risk of clinically significant disease or prostate would likely be acceptable to these men, their caregivers and health providers. PSA testing is already used in Australian practice and continues to be recommended for those who are not at higher risk

Feasibility

PSA testing is unlikely to be burdensome to men or the healthcare system. PSA testing is already used in Australian practice and continues to be recommended for those who are not at higher risk.

Rationale

The only randomised evidence found for PSA testing in higher risk men was a single subgroup analysis of the PLCO trial *[236]*. It supports testing for prostate cancer for men with an immediate family member diagnosed with prostate cancer, despite high levels of contamination in the control arm.

No areas of major debate about the evidence and the recommendations were identified, and full consensus was reached by the Working group.

Clinical question/ PICO

Population: Males with no history of prostate cancer who are at higher risk
Intervention: PSA testing
Comparator: No PSA testing

Summary

One article was found that reported the effects of PSA testing men with a higher risk of prostate cancer mortality in a randomised controlled trial; a subgroup analysis of participants in in the PLCO trial with an immediate family member diagnosed with prostate cancer *[236]*. In this higher risk

subgroup annual PSA testing using a threshold of 4 µg/L for 6 years starting at ages 55 to 74 plus annual DRE for the first 4 years, resulted in a clinically important reduction in prostate cancer mortality at 11 years when compared with usual care despite high levels of PSA testing in the control group. The certainty of this evidence was considered moderate due to concerns regarding imprecision.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No PSA testing	**Intervention** PSA testing	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer - specific deaths 11 years 9 Critical	Hazard ratio 0.49 (CI 95% 0.22 — 1.1) Based on data from 4,833 participants in 1 studies.	**62** per 10.000 Difference:	**31** per 10.000 **31 fewer per 10.000** (CI 95% 48 fewer — 6 more)	**Moderate** Downgraded one level due to serious concerns re imprecision	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.
Metastases at diagnosis or on progression		DRAFT No Evidence found.			

Consensus recommendation

5.5 In view of Strong recommendation 5.4 above, we propose offering males who are at higher risk PSA testing every two years from age 40 years.

- For males aged 40 to 49 years if total PSA is 1.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation.
- For males aged 50 to 69 years if total PSA is 2.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation.

Refer Section A: Risk assessment.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

Benefits/desirable effects

A single small (n = 4833) subgroup analysis of those with a family history (first degree relative) of prostate cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) reported a moderate decrease in prostate cancer

mortality at 11 years with annual PSA testing for 6 years plus annual DRE for the first 4 years starting at ages 55-74 years *[236]*. No evidence was found for any other screening protocols for high-risk male populations.

Harms/undesirable effects

The potential harms of PSA testing are well established for men with average risk disease. Clinical trials such as the European Randomised Study of Screening for Prostate Cancer (ERSPC) *[209]*, *[121]* and modelling studies *[195]* have shown that PSA testing leads to increased numbers of diagnoses, particularly of low-risk cancers and increased numbers of biopsies. Using multiparametric MRI to triage men with an elevated PSA level to biopsy as recommended in these Guidelines will reduce the number of unnecessary biopsies by approximately 50% and thereby reduce the detection of low-risk disease between 32-64% (see Specialist setting - Multiparametric magnetic resonance imaging). Offering active surveillance to men with lower risk prostate cancer as recommended in these Guidelines will reduce the number of men at risk of the long-term side effects of definitive treatments.

We are not aware of any evidence as to the magnitude of these harms for men at higher risk of prostate cancer mortality or clinically significant disease.

Balance of benefits and harms/desirable and undesirable effects

In the context of multiparametric MRI triage, active surveillance for men with lower risk localised disease, focal therapy and the improved management and prevention of treatment related morbidity which have substantially reduced the risks and harms of PSA testing in Australia, the moderate decrease in prostate cancer mortality would likely outweigh the potential harms associated with PSA testing for prostate cancer for higher risk men.

The evidence supports testing for prostate cancer for men with a first degree relative who has been diagnosed with prostate cancer. However, the protocol used in this single study was designed to reduce prostate cancer mortality in a general screening population rather than a population at higher risk of aggressive disease and prostate cancer mortality.

In the absence of evidence in higher risk populations for protocols specifically designed for higher risk men or any other protocols it is not possible to make evidence-based recommendations as to the optimal PSA testing protocol to use for higher risk men.

Certainty of the evidence

Moderate

The overall certainty of the evidence as to the whether the decrease in prostate cancer mortality with PSA testing for higher risk men was clinically important was rated moderate due to imprecision. The high risk of contamination in the control group and the high levels of PSA testing prior to the trial would likely lead to underestimates of the actual effect of PSA testing in this trial and were not considered serious concerns.

Values and preferences

No substantial variability expected

A systematic review found substantial variability as to how men valued a long-term reduction in risk of prostate cancer mortality and increased risk of unnecessary biopsies and treatment *[335]*. This evidence came from studies undertaken prior to the introduction of multiparametric MRI triage for biopsy and before active surveillance had become a routine management option for men with low-risk localised disease. This evidence is not reflective of contemporary practice in Australia. In the era of mpMRI triage, active surveillance, focal therapy and improved management and prevention of treatment related morbidity the risks and potential harms of PSA testing have been reduced. In this era, professional experience and consumer input point to most men at higher risk of prostate cancer mortality preferring PSA testing having regard to the long-term reduction in risk of prostate cancer mortality, reduction in risk of living with the syndrome of metastatic prostate cancer that may include treatment with androgen deprivation therapy (possible side effects-reduced libido and sexual function, fatigue, depression, hot flashes, increased risk of diabetes and its complications, and osteoporosis and fracture, and increased risk of cardiovascular disease), the reduced likelihood of requiring a biopsy and the reduced likelihood of undergoing unnecessary treatment of low risk disease. The high acceptance rates of active surveillance in Australia demonstrates that men are more comfortable living with untreated low risk cancer *[263]*. Males and their families place a higher value on an early diagnosis of prostate cancer compared to the morbidity of metastatic disease and premature death. They prefer to be able to make an informed decision of the management options of their prostate cancer having been diagnosed earlier and whilst curable.

Overwhelming clinical experience in the era of MRI and longer term active surveillance follow up demonstrating safety and efficacy is that there is minimal variability in men's acceptance of the PSA test once they have been informed of the benefits and potential harms. Furthermore, men with a family history of prostate cancer when compared to those men

without a family history are much more likely to seek testing having watched a loved one battle with living with metastatic prostate cancer and at times die from prostate cancer.

Resources and other considerations

No important issues with the recommended alternative

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

Offering PSA testing to men at higher risk of clinically significant disease or prostate would likely be acceptable to these men, their caregivers and health providers. PSA testing is already used in Australian practice and continues to be recommended for those who are not at higher risk

Feasibility

PSA testing is unlikely to be burdensome to men or the healthcare system. PSA testing is already used in Australian practice and continues to be recommended for those who are not at higher risk.

Rationale

The only randomised evidence found for PSA testing in higher risk men was a single subgroup analysis of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial) *[236]*. It supports testing for prostate cancer for men with an immediate family member diagnosed with prostate cancer. However, the PLCO protocol was designed to reduce prostate cancer mortality in a general screening population rather than a population at higher risk of aggressive disease and prostate cancer mortality.

In the absence of evidence in higher risk populations for protocols specifically designed for higher risk men or any other protocols it is not possible to make evidence-based recommendations as to the optimal PSA testing protocol to use for higher risk men.

Given the clear need for guidance as to how best to test high risk men to detect clinically important disease at an early stage we drafted Consensus Recommendations based on recent European and North American Guidelines consensus-based recommendations which recommend earlier and more frequent testing of high-risk men *[8]*, *[9]*, *[64]*.

No areas of major debate about the evidence and the recommendations were identified, and full consensus was reached by the Working group.

Clinical question/ PICO

Population: Males with no history of prostate cancer who are at higher risk
Intervention: PSA testing
Comparator: No PSA testing

Summary

One article was found that reported the effects of PSA testing men with a higher risk of prostate cancer mortality in a randomised controlled trial; a subgroup analysis of participants in in the PLCO trial with an immediate family member diagnosed with prostate cancer *[236]*. In this higher risk subgroup annual PSA testing using a threshold of 4 µg/L for 6 years starting at ages 55 to 74 plus annual DRE for the first 4 years, resulted in a clinically important reduction in prostate cancer mortality at 11 years when compared with usual care despite high levels of PSA testing in the control group. The certainty of this evidence was considered moderate due to concerns regarding imprecision.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No PSA testing	**Intervention** PSA testing	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer - specific deaths	Hazard ratio 0.49 (CI 95% 0.22 — 1.1)	62	31	**Moderate** Downgraded one	In a population of asymptomatic men at

Outcome Timeframe	**Study results and measurements**	**Comparator** No PSA testing	**Intervention** PSA testing	**Certainty of the evidence** (Quality of evidence)	**Summary**
11 years 9 Critical	Based on data from 4,833 participants in 1 studies.	per 10.000 Difference:	per 10.000 **31 fewer per 10.000** (CI 95% 48 fewer — 6 more)	level due to serious concerns re imprecision	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.
Metastases at diagnosis or on progression		No Evidence found.			

Consensus recommendation

5.6 Note that PSA testing recommendations for Aboriginal and Torres Strait Islander males are the same as for the general population.

- We propose offering Aboriginal and Torres Strait Islander males PSA testing every two years from age 50 to 69 years. If total PSA is 3.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation.
- We propose offering Aboriginal and Torres Strait Islander males who are not at a higher risk and who are interested in their prostate health an initial PSA test from age 40 years. If total PSA is 1.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation. If total PSA is less than 1.0 µg/L, no further PSA testing is recommended until age 50 years.
- We propose offering Aboriginal and Torres Strait Islander males aged 70 years and over a PSA test every two years subject to clinical assessment, which may include consideration of life expectancy, comorbidities, and patient values and preferences. If total PSA is 5.5 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation.
- We propose for Aboriginal and Torres Strait Islander males aged 70 years or over, if their PSA is less than 5.5 µg/L, continued testing be subject to clinical assessment, which may include consideration of life expectancy, comorbidities, and patient values and preferences.

For further details, refer to Section C: Priority populations

Review by 2030, subject to emerging evidence

Rationale

No evidence was found for PSA testing for Aboriginal and Torres Strait Islander males. It appears that these men have similar risks of prostate cancer mortality as Australian men who do not identify as Aboriginal or Torres Strait Islander peoples (see section 3.1). Consequently we have provided a consensus-based recommendation recommending that PSA testing for Aboriginal and Torres Strait islander men be the same as for the general population. For details refer to 3.1 Aboriginal and Torres Strait Islander males.

Conditional recommendation

5.7 We suggest offering PSA testing only to males whose life expectancy is greater than seven years.

Review by 2030, subject to emerging evidence

Rationale

This recommendation is from the 2016 Guidelines *[1]*. It is based on evidence from the ERSPC trial, in which there was a decrease in prostate cancer mortality with PSA screening. In this trial, a reduction in the risk of death from prostate cancer was first apparent at 6–7 years after the start of PSA testing *[209]*, *[353]*, *[354]*.

The Working Group agreed that as the evidence has not changed for this recommendation and that the recommendation is still current.

Consensus recommendation

5.8 We propose offering males who are not at a higher risk and who are interested in their prostate health an initial PSA test from age 40 years.

- In males aged 40 to 49 years, if total PSA is 1.0 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation.

If total PSA is less than 1.0 µg/L, no further PSA testing is recommended until age 50 years.

For further details, refer to Section A: Risk assessment.

Review by 2030, subject to emerging evidence

Rationale

The Working Group agreed that some men would be interested in PSA testing before the age of 50 years and that this was reasonable given the particularly devastating consequences of undetected aggressive disease for younger men, however, evidence-based recommendations were not possible as no randomised controlled trials were identified and a systematic review that compared PSA testing protocols with usual care for men aged 40-49 years, was not undertaken.

Instead, this recommendation was developed following review of the 2016 Guidelines recommendation taking into account that harm minimization has occurred with the introduction of mpMRI and the adoption of Active Surveillance for patients with low risk disease. To address this issue a consensus-based recommendation was developed based on the risks of prostate cancer mortality associated with a baseline PSA test result at ages 40-49 years *[379]*, *[380]*. Follow-up evidence from large cohort studies *[411]*, *[412]* reported that a large proportion of lethal prostate cancer in men aged between 40-49 years had baseline levels above the age-specific medians in their respective populations, and this risk was 4-fold when PSA levels ≥ 75th percentile (≥ 1.10 µg/L**)** *[380]*. This evidence suggests that men aged between 40 -49 years with PSA levels in the age specific 75th percentile are at higher risk of clinically significant cancers. The 75th percentile for Australian men aged between 40-49 years is typically 1.0 µg/L *[410]*, which was the basis for recommending this threshold of 1.0 µg/L here rather than. 1.1 µg/L.

Consensus recommendation

5.9 We propose offering males aged 70 years and over a PSA test every two years subject to clinical assessment, which may include consideration of life expectancy, comorbidities, and patient values and preferences. If total PSA is 5.5 µg/L or greater repeat the test within 1-3 months, and, if confirmed, consider referral and further investigation.

Review by 2030, subject to emerging evidence

Rationale

No randomised controlled trials were found to support evidence-based protocols for testing men aged over 70. There was strong community support for a recommendation in this age-group based on the public consultation we undertook *[204]*. The Working Group considered the need for consensus-based recommendations regarding the optimal protocol for men aged 70 years and above (refer 5.10 Consensus recommendation). The recommendation was based on a review of 2016 guidelines and also taking into account that harm minimization in this age group has occurred with the introduction of mpMRI and the adoption of Active Surveillance for patients with low risk disease. The Working Group agreed that 5.5 µg/L was an appropriate threshold after which further clinical assessment was suggested. Age-based PSA ranges were first proposed in 1993, with a reference range for the 95th percentile for men aged 70-79 proposed as 0-6.5 µg/L *[413]*. More recent evidence from ERSP shows that men aged over 70 who have previously undergone PSA testing have a very low risk of death from prostate cancer, particularly if their PSA level is below 5.5 µg/L *[415]*. The Australian Medicare Benefit Schedule currently sets a threshold of 5.5 ug/L for men aged over 70 to embark upon further investigation with free to total PSA ratios. Australian data on references ranges for PSA levels in men aged 70 and over may differ between groups from different ethnic backgrounds *[237]*.

Consensus recommendation

5.10 We propose for males aged 70 years or over, if their PSA is less than 5.5 µg/L, continued testing be subject to clinical assessment, which may include consideration of life expectancy, comorbidities, and patient values and preferences.

Review by 2030, subject to emerging evidence

Rationale

No randomised controlled trials were found to support evidence-based protocols for testing men aged over 70. There was strong community support for a recommendation in this age-group based on the public consultation we undertook *[204]*. The Working Group considered the need for consensus-based recommendations regarding the optimal protocol for men aged 70 years and above (refer 5.9 Consensus recommendation). The recommendation was based on a review of 2016 guidelines and also taking into account that harm minimization in this age group has occurred with the introduction of mpMRI and the adoption of Active Surveillance for patients with low risk disease. The Working Group agreed that 5.5 µg/L was an appropriate threshold after which further clinical assessment was suggested. Age-based PSA ranges were first proposed in 1993, with a reference range for the 95th percentile for men aged 70-79 proposed as 0-6.5 µg/L *[413]*. More recent evidence from ERSP shows that men aged over 70 who have previously undergone PSA testing have a very low risk of death from prostate cancer, particularly if their PSA level is below 5.5 µg/L *[415]*. The Australian Medicare Benefit Schedule currently sets a threshold of 5.5 ug/L for men aged over 70 to embark upon further investigation with free to total PSA ratios. Australian data on references ranges for PSA levels in men aged 70 and over may differ between groups from different ethnic backgrounds *[237]*.

Key message

5.11 To support awareness of prostate cancer risk factors for males aged 40 years and above, a national public education campaign focused on the importance of understanding risk factors and the early detection of prostate cancer is essential.

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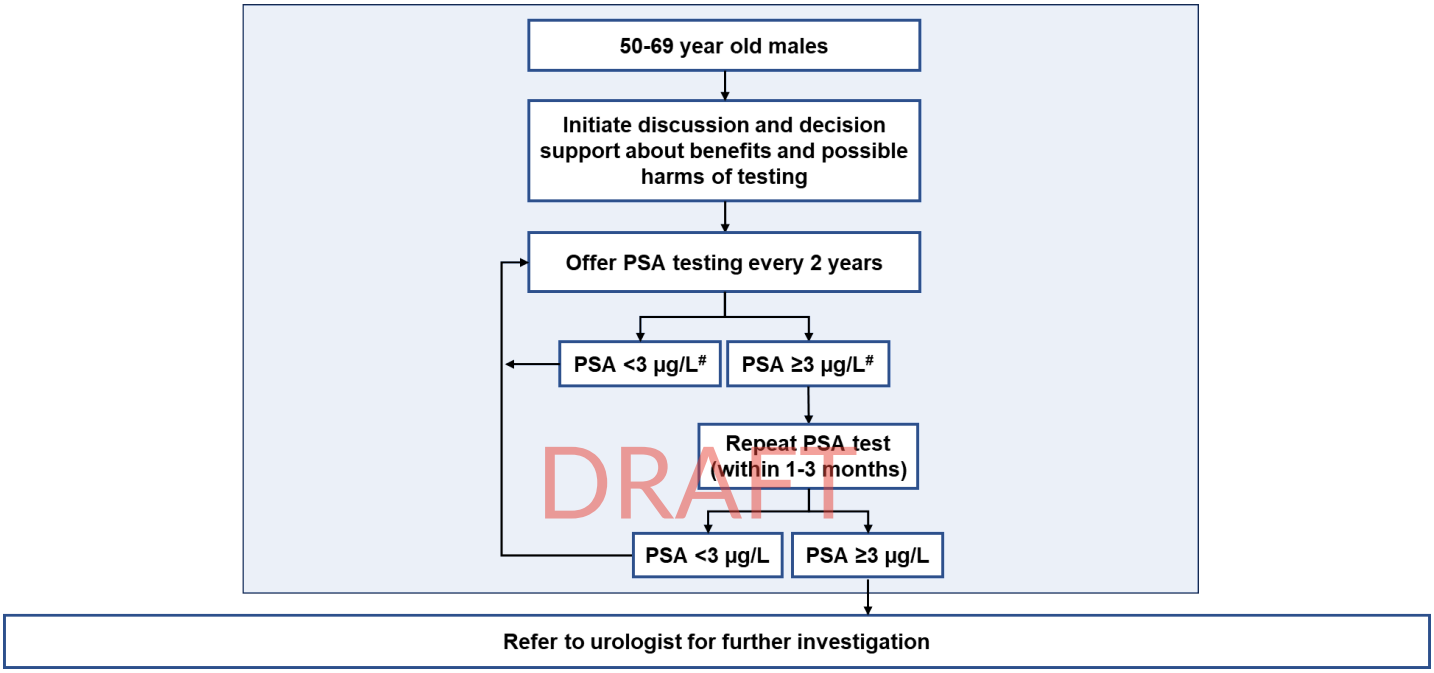
Flowcharts for PSA testing

Flowcharts reflecting the PSA testing recommendations have been developed to aid clinical decision making. Flowchart 1 in Section A: Risk assessment describes risk assessment for the early detection of prostate cancer in Australia.

The following flowcharts describe PSA testing in the primary care setting for:

- 50 to 69 year old males (flowchart 2)
- Males 70 years and over (flowchart 3)
- 40to 49 year old males (flowchart 4)
- Males at higher risk (flowchart 5)

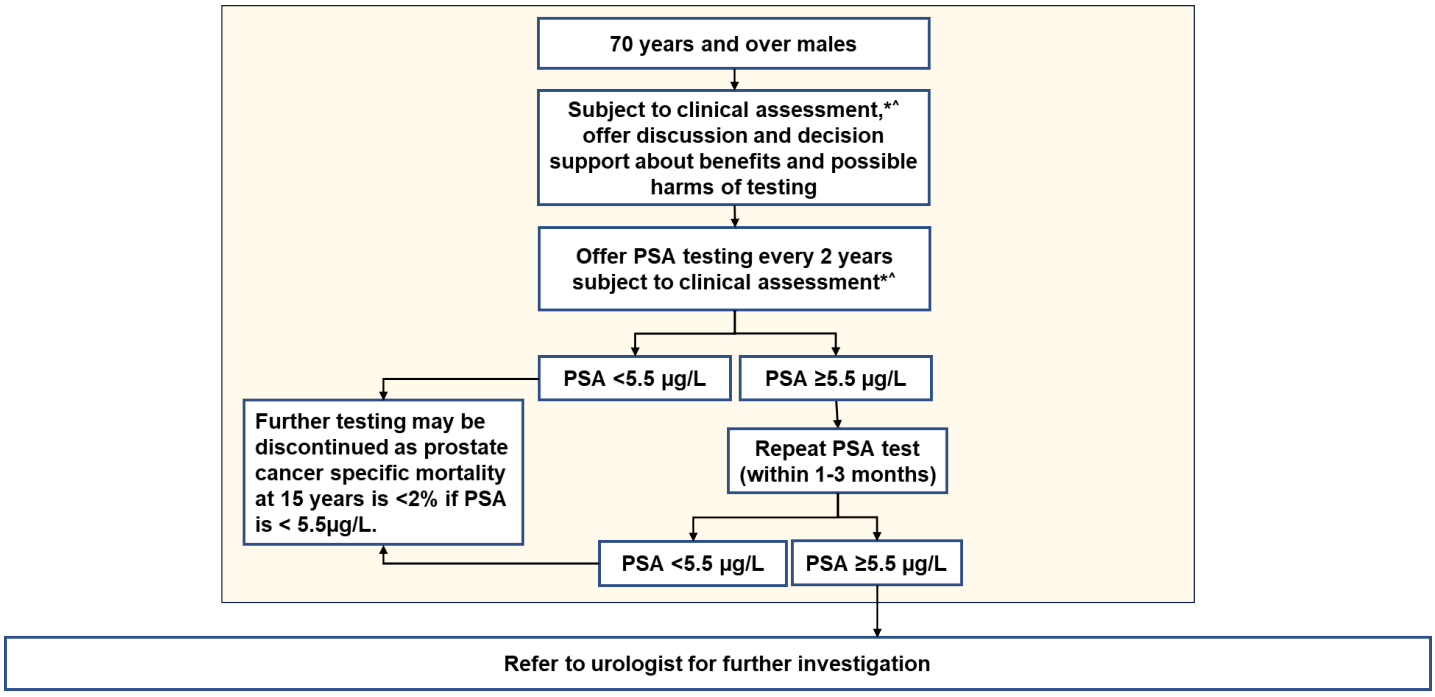
Flowchart 2: PSA testing of 50 to 69 year old males in the primary care setting



PSA ≥2 µg/L if significant family history of prostate cancer. Significant family history of prostate cancer = a brother diagnosed with prostate cancer, their father diagnosed with prostate cancer before the age of 65, or two or more second degree relatives who died of prostate cancer (refer Section A Risk assessment).

Higher risk includes, but is not restricted to, males with a brother or father diagnosed with prostate cancer, or two second degree relatives diagnosed with prostate cancer, Black males of sub-Saharan African ancestry and/or confirmed *BRCA2* gene mutations. Familial syndromes such as hereditary breast and ovarian cancer and Lynch syndrome are also associated with increased risk of clinically significant prostate cancer compared to the general population. (refer Section A Risk assessment).

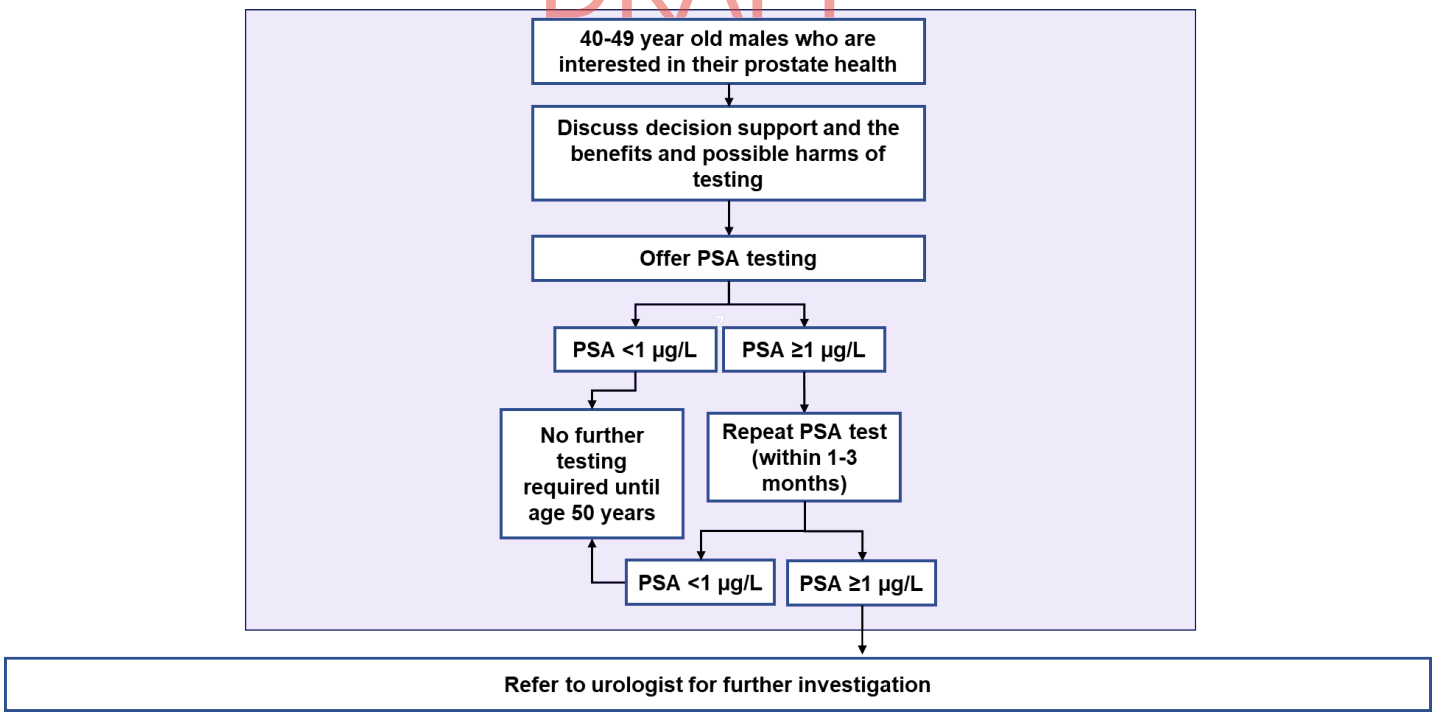
Flowchart 3: PSA testing of males 70 years and over in the primary care setting.



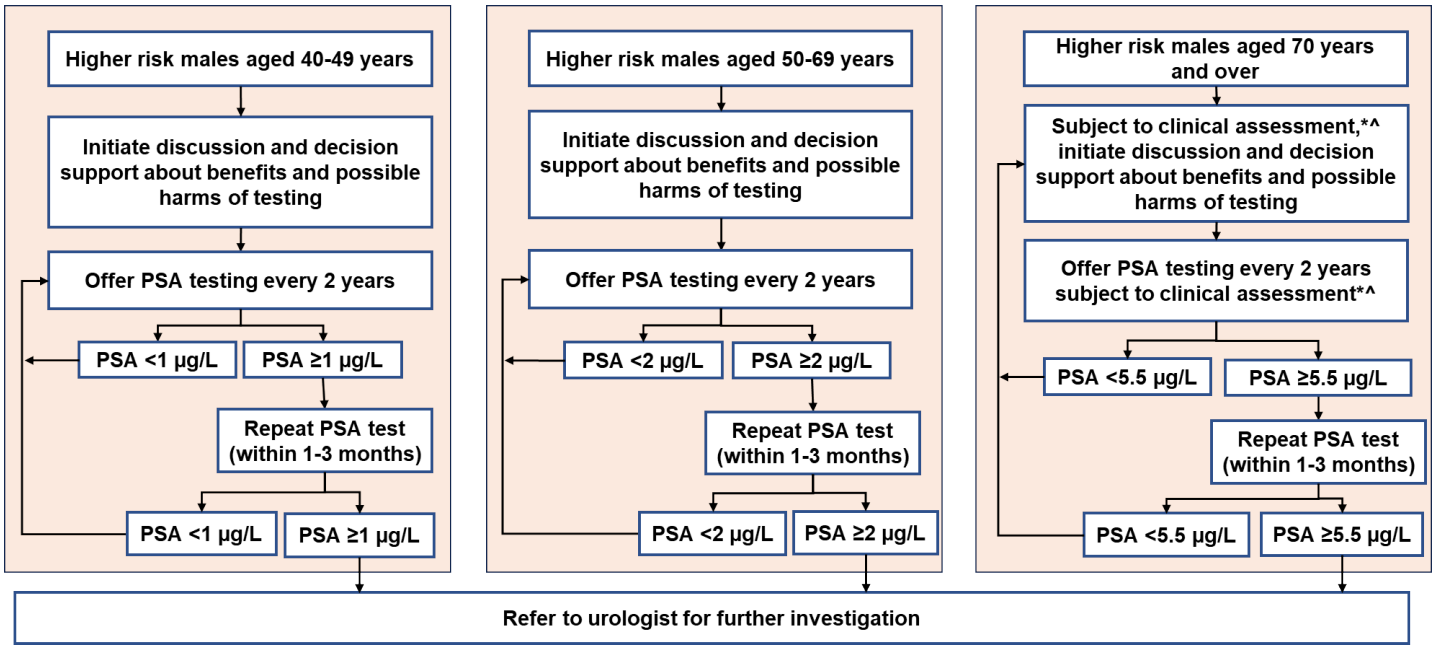
* Only offer testing if life expectancy is greater than 7 years.

^ Clinical assessment may include consideration of life expectancy, comorbidities, and patient values and preferences.

Flowchart 4: PSA testing of 40 to 49 year old males in the primary care setting



Flowchart 5: PSA testing of males at higher risk in the primary care setting



Higher risk includes, but is not restricted to, males with a brother or father diagnosed with prostate cancer, or two second degree relatives diagnosed with prostate cancer, Black males of sub-Saharan African ancestry and/or confirmed *BRCA2* gene mutations (refer Section 1.1). Familial syndromes such as hereditary breast and ovarian cancer and Lynch syndrome are also associated with increased risk of clinically significant prostate cancer compared to the general population.

* Only offer testing if life expectancy is greater than 7 years.

^ Clinical assessment may include consideration of life expectancy, comorbidities, and patient values and preferences.

6. Specialist setting - Multiparametric magnetic resonance imaging

Clinical Question

Can/should we use multiparametric MRI (mpMRI) to triage men with no history of prostate cancer and an elevated PSA for biopsy? (Clinical question 7)

Background

Since the 2016 Guidelines were published, a key shift in clinical practice for the early detection of prostate cancer involves the increasing use of multiparametric magnetic resonance imaging (mpMRI) in addition to PSA testing. MpMR is the addition of diffusion-weighted imaging (DWI) and dynamic contrast enhanced (DCE) sequences to high resolution T2-weighted sequences. Imaging can be performed on 1.5T or 3T magnets with slight preference for 3T in line with PI-RADS v2.1 *[319]*.

MRI Prostate protocol requires high resolution T2 weighted sequences performed in three planes, with DWI and DCE sequences performed in the axial plane. T1 sequences may also be performed. Emerging evidence suggests that biparametric MRI (bpMRI), which does not include DCE sequences may be adequate. However, this was not assessed in the Review, and the Guidelines do not provide a specific recommendation.

The clarity and precision of mpMRI enables the detection of suspicious lesions in the prostate which may harbour clinically significant prostate cancer (ISUP ≥ 2). In Australia, mpMRI is increasingly being used to inform decisions on who should progress to prostate biopsy and to guide the areas of the prostate to biopsy. It is also an important procedure used in active surveillance for monitoring prostate cancer.

The 2016 Guidelines only investigated the use of mpMRI for men who had already undergone a biopsy for prostate cancer which returned a negative result despite elevated PSA levels. This first line use of biopsy comes with a risk of overuse for men whose cancers are unlikely to be clinically significant cancer (ISUP < 2), a harm that mpMRI may be used to mitigate.

For the current update of the 2016 Guidelines, we considered the role of mpMRI prior to biopsy to determine if PSA levels in combination with mpMRI can help clinicians safely decide who should progress to biopsy and who should not.

Good practice statement

6.1 For males requiring further investigation on the basis of their PSA, an mpMRI is recommended as their next diagnostic test to determine if a biopsy is indicated.

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Conditional recommendation

6.2 We suggest offering prostate biopsy to males with an mpMRI suspicious of prostate cancer (Prostate Imaging Reporting and Data System [PI-RADS] 4-5).

We suggest offering prostate biopsy to males with an equivocal PI-RADS 3 mpMRI and PSA density (PSAD) ≥ 0.15 µg/L/mL.

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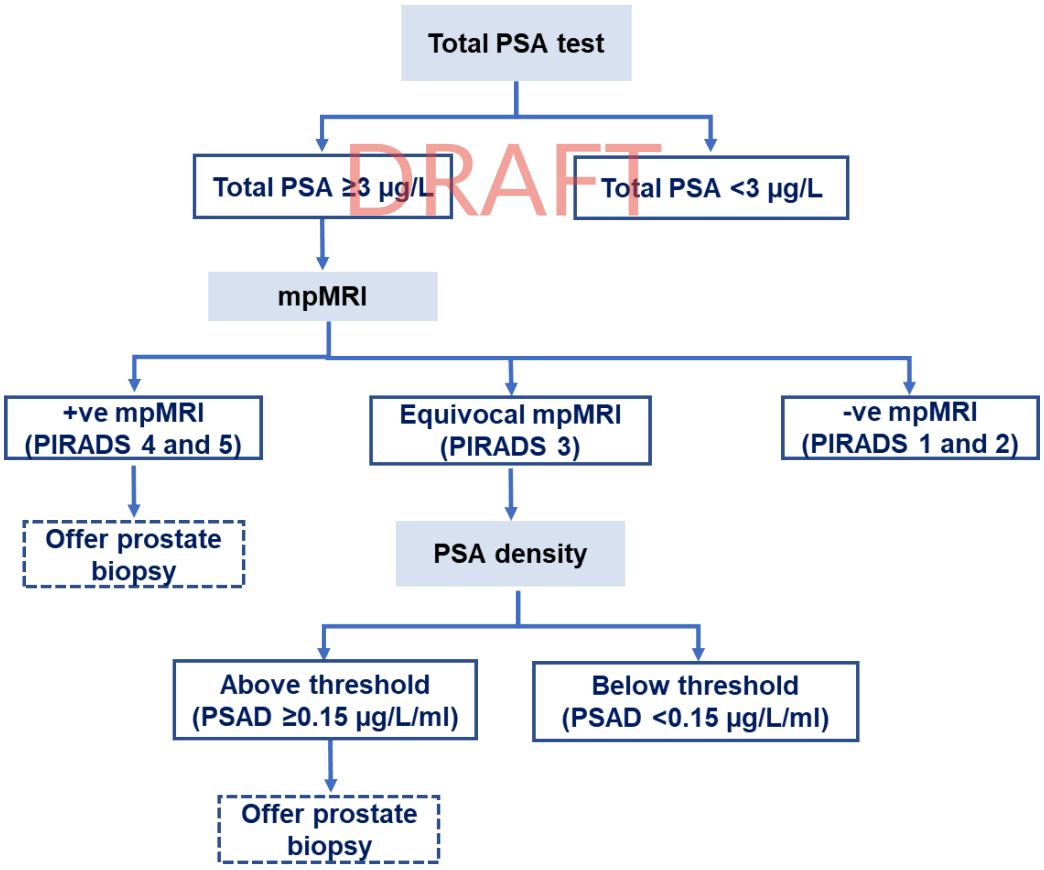
Practical info

Suggested triage protocol using mpMRI



Evidence to decision

Benefits and harms Substantial net benefits of the recommended alternative

Benefits/desirable effects

If the prevalence of ISUP Grade ≥ 2 disease is 20% and the prevalence of ISUP Grade 1 disease is 20% the number of unnecessary biopsies avoided is:

- **Large** if do not biopsy those with:
  - PI-RADS 1-3 (5 studies *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*)
  - PI-RADS 1-2 or PI-RADS 3 and PSAD< 0.15 µg/L/mL (2 studies*[48]*, *[49]*)
  - PI-RADS 1-3 and PSAD < 0.20 µg/L/mL (1 study *[48]*)
  - PI-RADS 1-2 or PI-RADS 3 and PSAD < 0.20 µg/L/mL (1 study *[48]*)
- **Moderate** if do not biopsy those with:
  - PI-RADS 1-2 (5 studies *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*)
  - PI-RADS 1-2 and PSAD < 0.15 µg/L/mL (2 studies *[48]*, *[49]*)
  - PI-RADS 1-3 and PSAD < 0.15 µg/L/mL (2 studies *[48]*, *[49]*)

The number of ISUP Grade 1 cancers undetected is:

- **Clinically unimportant (trivial)** if do not biopsy those with
  - PI-RADS 1-2 (3 studies *[48]*, *[50]*, *[51]*, *[52]*)
- **Small but clinically important** number undetected if do not biopsy those with
  - PI-RADS 1-3 (2 studies *[48]*, *[51]*, *[52]*)

Overall, the reduction in detection in ISUP Grade 1 cancer is trivial or low (depending on the mpMRI triage protocol used), but the reduction in unnecessary biopsies is large for most protocols – in fact, around half of unnecessary biopsies could be avoided using two of the protocols. This is a major harm reduction in testing for prostate cancer as biopsy is an invasive procedure with its own risks and costs.

Another practical benefit of using mpMRI to triage for biopsy is that when it is positive, it enables precise targeting of the visible lesion at biopsy.

Harms/ undesirable effects

If the prevalence of ISUP Grade ≥ 2 disease is 20% the number of ISUP Grade ≥ 2 (clinically significant) cancers undetected is:

- **Clinically unimportant (trivial)** if do not biopsy those with:
  - PI-RADS 1-2 (5 studies *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*)
  - PI-RADS 1-3 and PSAD < 0.15 µg/L/mL (2 studies*[48]*, *[49]*) or PSAD < 0.20 µg/L/mL (1 study *[48]*)
  - PI-RADS 1-2 or PI-RADS 3 and PSAD < 0.15 µg/L/mL (2 studies*[48]*, *[49]*) or PSAD < 0.20 µg/L/mL (1 study *[48]*)
- **Borderline small but clinically important** if do not biopsy all those with:
  - PI-RADS 1-3 (5 studies *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*)

If prevalence of ISUP Grade ≥ 3 disease is 10% or 20% the number of ISUP grade 3 cancers undetected is:

- **Clinically unimportant (trivial)** if do not biopsy those with PI-RADS 1-3 (4 studies *[48]*, *[49]*, *[51]*, *[52]*, *[53]*)

No evidence from RCTs was found for metastases or prostate cancer mortality.

Trivial to small numbers of clinically significant cancers, and even smaller numbers of ISUP Grade ≥ 3 prostate cancers would be initially undetected using mpMRI triage. The harms are therefore trivial or small (depending on the mpMRI triage protocol) and are further mitigated by ensuring patients have further follow-up with a PSA test which can then enable detection if risk increases over time.

Balance of benefits and harms/ desirable and undesirable effects

Evidence was found for a range of different mpMRI triage protocols. The evidence suggests that for men with negative mpMRI (PI-RADS 1-2) the number of significant cancers initially undetected is clinically unimportant and it is therefore acceptable to avoid a biopsy for these men.

For men with mpMRI PI-RADS 4-5, the evidence suggests that the number of significant cancers initially undetected is borderline clinically important and it would therefore not be acceptable to avoid a biopsy for these men. For PI-RADS 3 (equivocal) lesions, where there is uncertainty about the presence of clinically significant disease, the addition of PSAD can be used as a harm minimisation tool to identify those more likely to benefit from undergoing biopsy.

Of the protocols considered for which there was evidence from more than one study, avoiding biopsy for those with PI-RADS of 1-2 or those with PI-RADS 3 and a PSAD < 0.15 µg/L/mL offered the largest reduction (around 50%) in unnecessary biopsies (benefits) for a trivial increase in undetected clinically significant disease (harms). For those who

do not have immediate biopsy, any harms can be mitigated through appropriate monitoring with PSA testing and/or mpMRI.

The large benefit of around half of all biopsies being avoided because they are unnecessary far outweighs the small risk of initially undetected significant cancer.

Certainty of the evidence

Low

Evidence was found for a range of different triage protocols. The certainty of the evidence for most triage protocols, including the recommended protocol, for most outcomes was moderate. However, all the evidence relates to the diagnostic accuracy of significant cancer, not subsequent clinical outcomes.

As evidence for clinical outcomes such as rates of metastases and death is lacking, the overall certainty of the evidence was rated low for these protocols.

The certainty of the evidence for the detection of clinically significant disease was low for one of the five protocols based on evidence from more than one study *[48]*, *[49]*. In the absence of evidence for patient important outcomes, certainty of the evidence for this protocol was rated very low.

Values and preferences

No substantial variability expected

We believe most people would prefer to avoid an unnecessary invasive biopsy in the knowledge that the risk of missing a clinically significant cancer is small and that any risk can be mitigated through appropriate monitoring with PSA testing and/or mpMRI.

Resources and other considerations

No important issues with the recommended alternative

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

In the Goteborg-2 trial participants reported that MRI was less bothersome than prostate biopsy *[54]*. We believe that in Australia using mpMRI to determine if biopsy is indicated is more acceptable than proceeding to invasive biopsy on the basis of elevated PSA levels alone.

Feasibility

We believe that the intervention is feasible, as metropolitan areas in Australia have excellent access to appropriate mpMRI services. However, regional and remote men may be required to travel long distances to access mpMRI.

The use of PSA density is highly feasible as it is calculated using the PSA level and prostate volume which is reported by the mpMRI, i.e. no additional testing is required.

mpMRI and PSA density measurements are less burdensome to patients than an invasive biopsy which involves hospital admission and associated risks.

Rationale

For this recommendation, several protocols were examined to determine if mpMRI could be used to triage men with no history of prostate cancer and an elevated PSA for prostate biopsy. Overall, the evidence suggested that avoiding biopsy for those with a PI-RADS of 1 or 2 or a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL offered the largest reduction (around 50%) in unnecessary biopsies (benefits) for a trivial increase in undetected clinically significant disease (harms). For those who do not have immediate biopsy, any harms can be mitigated through appropriate monitoring with PSA testing and/or mpMRI. Therefore, we concluded that the large benefit of mpMRI triage in reducing the number of unnecessary biopsies performed outweighs the small risk of initially undetected significant cancer.

The studies examined all related to diagnostic accuracy and not clinical outcomes. We did not find evidence for the effect of mpMRI triage on clinical outcomes (prostate cancer mortality, overall mortality and metastatic disease) and as a result the overall certainty of the evidence was downgraded. This remains an area of focus as evidence becomes available in the future.

No areas of major debate about the evidence and this recommendation were identified. This recommendation was reached with full consensus.

Clinical question/ PICO

Population: Men with no history of prostate cancer and elevated PSA levels (biopsy naïve)
Intervention: mpMRI triage to biopsy
Comparator: No mpMRI triage to biopsy – all men with elevated PSA levels undergo biopsy

Summary

Five studies were identified that investigated the use of mpMRI alone to triage men with elevated PSA levels to prostate biopsy *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*. Findings from one of the studies, the PROMIS study, were published in 2017 *[51]* and 2020 *[52]*. A meta-analysis of the results from these studies showed that mpMRI could be used to triage men to biopsy. Men with mpMRI PI-RADS 1 or 2 lesions are unlikely to need a biopsy as the number of clinically significant cancers undetected is not clinically important (< 50/1000). If men with PI-RADS 1, 2 or 3 lesions are not biopsied, there is the possibility that a small (50 -100/1000) but clinically important number of clinically significant cancers may not be detected. Consequently, biopsy is required for men with PI-RADS 4 and 5 lesions and for at least some men with PI-RADS 3 lesions.

If the prevalence of clinically insignificant (ISUP grade 1) cancer is 20%, it is estimated that 63.5% (127/200) of clinically insignificant cancer will not be detected if men with a PI-RADS 1, 2 or 3 lesions are not biopsied, and 32% (64/200) of clinically insignificant cancer will not be detected if men with a PI-RADS 1 or 2 lesions are not biopsied.

The certainty of evidence was moderate or low. All five studies had a high risk of selection bias as in each of these studies it was considered likely that not all men with an elevated PSA were offered mpMRI. In addition, there were serious concerns as to whether the number of clinically significant cancers undetected is small if men with PI-RADS 1, 2 or 3 lesions do not undergo biopsy as the 95% confidence interval included clinically unimportant differences.

Note: the evidence in this PICO informed conditional recommendations 6.2 and 6.3.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 23 (95%CI:18, 28) based on a summary sensitivity of 0.887 (0.86, 0.91).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2 the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20%	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 51 (95%CI:46, 58) based on a summary sensitivity of 0.744 (0.71, 0.77).		**Low** Downgraded by two levels due to serious concerns re potential selection bias and imprecision	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade ≥ 2 prostate cancers maybe small but clinically important.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
8 Critical					
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 339 (95%CI:312, 368) based on a summary specificity of 0.424 (0.39, 0.46)		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2 the number of unnecessary biopsies avoided is likely moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 585 (95%CI:560, 608) based on a summary specificity of 0.731 (0.70, 0.76)		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-3 the number of unnecessary biopsies avoided is likely large.
ISUP Grade ≥ 3 prostate cancer not detected where the prevalence of ISUP Grade ≥ 3 disease is 20% 8 Critical	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of undetected ISUP Grade ≥ 3 prostate cancers in a population of 1000 men with elevated PSA levels is 10 (95%CI:6, 16) based on a summary sensitivity of 0.949 (0.92, 0.97).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2 the number of undetected ISUP Grade ≥ 3 prostate cancers is likely clinically unimportant.
ISUP Grade ≥ 3 prostate cancer not detected where the prevalence of ISUP Grade ≥ 3 disease is 20% 8 Critical	Based on data from 1,696 participants in 4 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected ISUP Grade ≥ 3 prostate cancers in a population of 1000 men with elevated PSA levels is 21 (95%CI:14, 30) based on a summary sensitivity of 0.897 (0.85, 0.93).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade ≥ 3 prostate cancers is likely clinically unimportant.
ISUP Grade 1 prostate cancer not detected	Based on data from 1,546 participants in 3 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of undetected		**Moderate** Downgraded by one level due to	If do not biopsy men with a PI-RADS of 1-2 the number of undetected ISUP Grade

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
where the prevalence of ISUP Grade 1 disease is 20% 7 Critical		ISUP Grade 1 prostate cancers in a population of 1000 men with elevated PSA levels is 64 (95%CI:54, 76) based on a summary sensitivity of 0.675 (0.62, 0.73).		serious concerns re potential selection bias	1 prostate cancers is likely clinically unimportant.
ISUP Grade 1 prostate cancer not detected where the prevalence of ISUP Grade 1 disease is 20% 7 Critical	Based on data from 1,383 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected ISUP Grade 1 prostate cancers in a population of 1000 men with elevated PSA levels is 127 (95%CI:114, 138) based on a summary sensitivity of 0.366 (0.31, 0.43).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade 1 prostate cancers is likely small but clinically important.

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Clinical question/ PICO

Population: Men with no history of prostate cancer with elevated PSA levels (biopsy naïve)
Intervention: mpMRI triage to biopsy
Comparator: No mpMRI triage to biopsy – all men with elevated PSA levels undergo biopsy

Summary

This PICO examined the effect of mpMRI triage on patient relevant outcomes, specifically all-cause mortality, prostate cancer mortality or metastases as well as cancer detection outcomes. Systematic searches of the literature did not identify any randomised controlled trial evidence for this PICO.

This question remains an area of interest. Searches of clinical trial registries and literature searches identified three potentially relevant ongoing trials. Research in this area will be monitored and the Guidelines revised as new relevant data becomes available.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy	**Certainty of the evidence** (Quality of evidence)
All cause mortality, prostate cancer mortality or metastasis		No relevant randomised controlled trials identified.		
ISUP grade ≥ 2 prostate cancer detection, or ISUP grade 1 prostate cancer detection, or biopsy rates		No relevant randomised controlled trials identified.		

Clinical question/ PICO

Population: Men with no history of prostate cancer and elevated PSA levels who are biopsy naïve and mpMRI negative and do not undergo biopsy.

Intervention: Follow-up protocol

Comparator: Another follow-up protocol or no specific follow-up

Summary

This PICO examined the effect of follow-up protocols to detect clinically significant prostate cancer in men who are MRI negative and did not undergo biopsy. Systematic searches of the literature did not identify any RCT evidence for the effect of different the different follow-up protocols for these men on disease outcomes, specifically all-cause mortality, prostate cancer mortality or metastasis.

This question remains an area of interest. Searches of clinical trial registries and literature searches identified three potentially relevant ongoing trials. Research in this area will be monitored and the Guidelines revised as new relevant data becomes available.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** Another follow-up protocol or no specific follow-up	**Intervention** Follow-up protocol	**Certainty of the evidence** (Quality of evidence)
All cause mortality, prostate cancer mortality or metastasis		No suitable studies found		

Clinical question/ PICO

Population: Men with no history of prostate cancer with elevated PSA levels (biopsy naïve)
Intervention: Triage to biopsy using mpMRI with or without PSA density using a threshold of 0.15 µg/L/mL
Comparator: No mpMRI triage to biopsy – all men with elevated PSA levels undergo biopsy

Summary

This PICO compares the diagnostic accuracy of mpMRI plus PSA density with that of mpMRI alone for the detection of clinically significant prostate cancer in biopsy naïve men to determine whether PSA density might be used to distinguish a subgroup of individuals with an equivocal PI-RADS 3 lesion who might not require an immediate biopsy.

Two studies were found that met the criteria for inclusion in our systematic review *[48]*, *[49]*. Meta-analyses of their results enabled the comparison of outcomes for a range of different triage protocols when compared with no triage within the same cohorts. For individuals with a PI-RADS less than 4, protocols offering biopsies only to those with a PSA density ≥ 0.15 µg/L/mL are estimated to result in a clinically unimportant (< 50) undetected clinically significant (ISUP Grade ≥ 2) cancers in a population of 1000 men with elevated PSA levels. The largest number of unnecessary biopsies are avoided if only those with mpMRI PI-RADS 3 and a PSA density ≥ 0.15 µg/L/mL undergo biopsy. The certainty of the evidence for this protocol was moderate due to concerns regarding selection bias.

More information can be found in the Technical Report.

Note: the evidence in this PICO informed conditional recommendations 6.2 and 6.3.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy with/without PSAD ≥ 0.15 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2** who have a **PSAD < 0.15 µg/L/mL** the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 11 (95%CI: 8, 16) based on a summary sensitivity of 0.947 (0.92, 0.96).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2 who have a PSAD < 0.15 µg/L/mL the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy with/without PSAD ≥ 0.15 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.15 µg/L/mL** the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 23 (95%CI: 18, 30) based on a summary sensitivity of 0.884 (0.85, 0.91).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS 1-3 who have a PSAD < 0.15 µg/L/mL the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2**, the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 23 (95%CI:18, 30) based on a summary sensitivity of 0.884 (0.85, 0.91).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2, the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.15 µg/L/mL** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 36 (95%CI:28, 44) based on a summary sensitivity of 0.822 (0.78, 0.86).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL, the number of undetected ISUP Grade ≥ 2 prostate cancers may be clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20%	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 47 (95%CI:40, 56) based on a summary sensitivity of 0.766 (0.72, 0.80).		**Low** Downgraded by two levels due to serious concerns re potential selection bias and imprecision.	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade ≥ 2 prostate cancers may be clinically unimportant.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy with/without PSAD ≥ 0.15 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
8 Critical					
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2** who have a **PSAD < 0.15 µg/L/mL** the number of unnecessary biopsies avoided in a population of 1000 asymptomatic individuals with elevated PSA levels is 226 (95%CI: 200, 256) based on a summary specificity of 0.283 (0.25, 0.32).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2 who have a PSAD < 0.15 µg/L/mL the number of unnecessary biopsies avoided is likely moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.15 µg/L/mL** the number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 373 (95%CI: 336, 408) based on a summary specificity of 0.466 (0.42, 0.51).		**Low** Downgraded by two levels due to serious concerns re potential selection bias and imprecision.	If do not biopsy men with a PI-RADS 1-3 who have a PSAD < 0.15 µg/L/mL the number of unnecessary biopsies avoided may be moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 354 (95%CI:320, 392) based on a summary specificity of 0.443 (0.40, 0.49).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2 the number of unnecessary biopsies avoided is likely moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.15 µg/L/mL** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 500 (95%CI:464, 536) based on a summary specificity of 0.625 (0.58, 0.67).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL, the number of unnecessary biopsies avoided is likely large.
Unnecessary biopsies avoided where the prevalence of	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of unnecessary biopsies avoided in a population of 1000		**Moderate** Downgraded by one level due to serious concerns re	If do not biopsy men with a PI-RADS of 1-3 the number of unnecessary biopsies avoided is likely large.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy with/without PSAD ≥ 0.15 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
clinically significant disease is 20% 7 Critical		men with elevated PSA levels is 566 (95%CI:536, 592) based on a summary specificity of 0.707 (0.67, 0.74)		potential selection bias.	

Clinical question/ PICO

Population: Men with no history of prostate cancer with elevated PSA levels (biopsy naïve)
Intervention: Triage to biopsy using mpMRI with or without PSA density using a threshold of 0.15 or 0.20 µg/L/mL
Comparator: No mpMRI triage to biopsy – all men with elevated PSA levels undergo biopsy

Summary

For this PICO one study was found that compared diagnostic accuracy outcomes using mpMRI and PSAD thresholds of 0.15 and 0.20 µg/L/mL to triage men to biopsy *[48]*. In this study if men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSA density < 0.15 µg/L/mL were not biopsied the number of undetected clinically significant cancers was likely clinically unimportant (< 50/1000) whereas if a PSA density threshold of 0.20 µg/L/mL was used the number of undetected clinically significant cancers was higher and it was less certain whether the number would be clinically unimportant.

More information can be found in the Technical Report.

Note: the evidence in this PICO informed conditional recommendations 6.2 and 6.3.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy with/without PSAD 0.15 or 0.20 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.15 µg/L/mL** the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 25 (95%CI: 18, 32) based on a summary sensitivity of 0.875 (0.84, 0.91).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-3 who have a PSAD < 0.15 µg/L/mL the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.
Clinically significant (ISUP Grade ≥ 2)	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.20 µg/L/mL**		**Moderate** Downgraded by one level due to	If do not biopsy men with a PI-RADS 1-3 who have a PSAD < 0.20 µg/L/mL the

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy with/without PSAD 0.15 or 0.20 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical		the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 34 (95%CI: 26, 42) based on a summary sensitivity of 0.829 (0.79, 0.87).		serious concerns re potential selection bias.	number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.15 µg/L/mL** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 38 (95%CI:30, 46) based on a summary sensitivity of 0.811 (0.77, 0.85).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL, the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.20 µg/L/mL** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 42 (95%CI:34, 52) based on a summary sensitivity of 0.788 (0.74, 0.83).		**Low** Downgraded by two levels due to serious concerns re potential selection bias and imprecision.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.20 µg/L/mL, the number of undetected ISUP Grade ≥ 2 prostate cancers may be clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 48 (95%CI:40, 58) based on a summary sensitivity of 0.758 (0.71, 0.83).		**Low** Downgraded by two levels due to serious concerns re potential selection bias and imprecision.	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade ≥ 2 prostate cancers may be clinically unimportant.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy with/without PSAD 0.15 or 0.20 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.15 µg/L/mL** the number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 376 (95%CI: 336, 416) based on a summary specificity of 0.470 (0.42, 0.52).		**Low** Downgraded by two levels due to serious concerns re potential selection bias and imprecision.	If do not biopsy men with a PI-RADS of 1-3 who have a PSAD < 0.15 µg/L/mL the number of unnecessary biopsies avoided may be moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.20 µg/L/mL** the number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 482 (95%CI: 440, 520) based on a summary specificity of 0.602 (0.55, 0.65).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS 1-3 who have a PSAD < 0.20 µg/L/mL the number of unnecessary biopsies avoided is likely large.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-2** or men with a **PI-RADS of 3 and a PSAD < 0.15 µg/L/mL** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 505 (95%CI:464, 544) based on a summary specificity of 0.631 (0.58, 0.68).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2 , or men with a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL, the number of unnecessary biopsies avoided is likely large.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.20 µg/L/mL** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 542 (95%CI:504, 576) based on a summary specificity of 0.677 (0.63, 0.72).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.20 µg/L/mL, the number of unnecessary biopsies avoided is likely large.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20%	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of unnecessary biopsies avoided in a population of 1000 asymptomatic individuals with elevated PSA levels is 566 (95%CI:528, 600) based on a summary specificity of 0.708 (0.66, 0.75)		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-3 the number of unnecessary biopsies avoided is likely large.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy with/without PSAD 0.15 or 0.20 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
7 Critical					

Conditional recommendation

6.3 We suggest that males with an equivocal PI-RADS 3 mpMRI and PSAD < 0.15 µg/L/mL may not require prostate biopsy subject to clinical assessment.

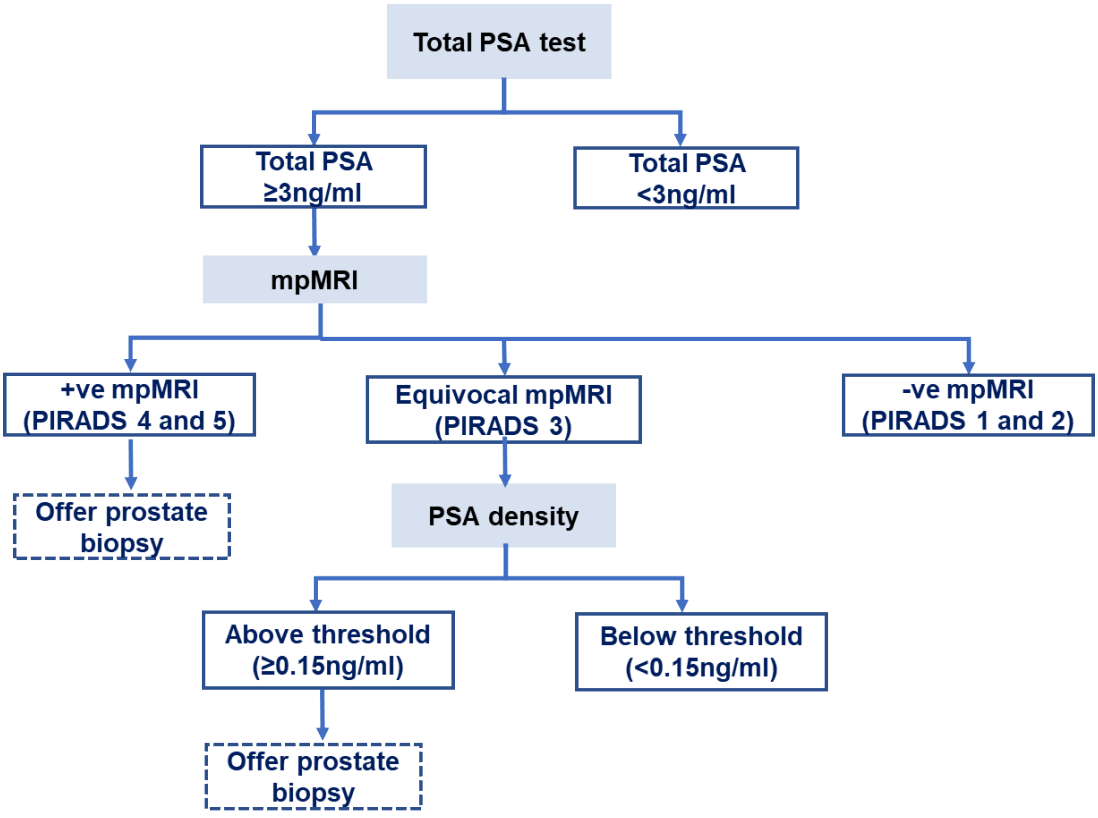
We suggest that males with an mpMRI not suspicious of prostate cancer (PI-RADS 1-2) may not require prostate biopsy subject to clinical assessment.

*For males who do not require biopsy, refer 6.4 Consensus recommendation.

Review by 2030, subject to emerging evidence

Practical info

Suggested triage protocols using mpMRI



Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

Benefits/desirable effects

If the prevalence of ISUP Grade ≥ 2 disease is 20% and the prevalence of ISUP Grade 1 disease is 20% the number of unnecessary biopsies avoided is:

- **Large** if do not biopsy those with:
  - PI-RADS 1-3 (5 studies *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*)
  - PI-RADS 1-2 or PIRADS 3 and PSAD< 0.15 (2 studies*[48]*, *[49]*)
  - PI-RADS 1-3 and PSAD < 0.20 (1 study *[48]*)
  - PI-RADS 1-2 or PIRADS 3 and PSAD < 0.20 (1 study *[48]*)
- **Moderate** if do not biopsy those with:
  - PI-RADS 1-2 (5 studies *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*)
  - PI-RADS 1-2 and < 0.15 (2 studies *[48]*, *[49]*)
  - PI-RADS 1-3 and PSAD < 0.15 (2 studies *[48]*, *[49]*)

The number of ISUP Grade 1 cancers undetected is:

- **Clinically unimportant (trivial)** if do not biopsy those with
  - PI-RADS 1-2 (3 studies *[48]*, *[50]*, *[51]*, *[52]*)
- **Small but clinically important** number undetected if do not biopsy those with
  - PI-RADS 1-3 (2 studies *[48]*, *[51]*, *[52]*)

Overall, the reduction in detection in ISUP grade 1 cancer is trivial or low (depending on the mpMRI triage protocol used), but the reduction in unnecessary biopsies is large for most protocols – in fact, around half of unnecessary biopsies could be avoided using two of the protocols. This is a major harm reduction in testing for prostate cancer as biopsy is an invasive procedure with its own risks and costs.

Another practical benefit of using mpMRI to triage for biopsy is that when it is positive, it enables precise targeting of the visible lesion at biopsy.

Harms/ undesirable effects

If the prevalence of ISUP Grade ≥ 2 disease is 20% the number of ISUP Grade ≥ 2 (clinically significant) cancers undetected is:

- **Clinically unimportant (trivial)** if do not biopsy those with:
  - PI-RADS 1-2 (5 studies *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*)
  - PI-RADS 1-3 and PSAD < 0.15 (2 studies*[48]*, *[49]*) or < 0.20 (1 study *[48]*)
  - PI-RADS 1-2 or PIRADS 3 and PSAD < 0.15 (2 studies*[48]*, *[49]*) or < 0.20 (1 study *[48]*)
- **Borderline small but clinically important** if do not biopsy all those with:
  - PI-RADS 1-3 (5 studies *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*)

If prevalence of ISUP Grade ≥ 3 disease is 10% or 20% the number of ISUP grade 3 cancers undetected is:

- **Clinically unimportant (trivial)** if do not biopsy those with PIRADS 1-3 (4 studies *[48]*, *[49]*, *[51]*, *[52]*, *[53]*)

No evidence from RCTs was found for metastases or prostate cancer mortality.

Trivial to small numbers of clinically significant cancers, and even smaller numbers of ISUP ≥ 3 prostate cancers would be initially undetected using mpMRI triage. The harms are therefore trivial or small (depending on the mpMRI triage protocol) and are further mitigated by ensuring patients have further follow-up with a PSA test which can then enable detection if risk increases over time.

Balance of benefits and harms/ desirable and undesirable effects

Evidence was found for a range of different mpMRI triage protocols. The evidence suggests that for men with negative mpMRI (PI-RADS 1-2) the number of significant cancers initially undetected is clinically unimportant and it is therefore acceptable to avoid a biopsy for these men.

For men with mpMRI PI-RADS 4-5, the evidence suggests that the number of significant cancers initially undetected is borderline clinically important and it would therefore not be acceptable to avoid a biopsy for these men. For PI-RADS 3

(equivocal) lesions, where there is uncertainty about the presence of clinically significant disease, the addition of PSAD can be used as a harm minimisation tool to identify those more likely to benefit from undergoing biopsy.

Of the protocols considered for which there was evidence from more than one study, avoiding biopsy for those with PI-RADS of 1-2 or those with PI-RADS 3 and a PSAD < 0.15 µg/L/mL offered the largest reduction (around 50%) in unnecessary biopsies (benefits) for a trivial increase in undetected clinically significant disease (harms). For those who do not have immediate biopsy, any harms can be mitigated through appropriate monitoring with PSA testing and/or mpMRI.

The large benefit of around half of all biopsies being avoided because they are unnecessary far outweighs the small risk of initially undetected significant cancer.

Certainty of the evidence

Low

Evidence was found for a range of different triage protocols. The certainty of the evidence for most triage protocols, including the recommended protocol, for most outcomes was moderate. However, all the evidence relates to the diagnostic accuracy of significant cancer, not subsequent clinical outcomes.

As evidence for clinical outcomes such as rates of metastases and death is lacking, the overall certainty of the evidence was rated low for these protocols.

The certainty of the evidence for the detection of clinically significant disease was low for one of the five protocols based on evidence from more than one study *[48]*, *[49]*. In the absence of evidence for patient important outcomes, certainty of the evidence for this protocol was rated very low.

Values and preferences

No substantial variability expected

We believe most people would prefer to avoid an unnecessary invasive biopsy in the knowledge that the risk of missing a clinically significant cancer is small and that any risk can be mitigated through appropriate monitoring with PSA testing and/or mpMRI.

Resources and other considerations

No important issues with the recommended alternative

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

In the Goteborg-2 trial participants reported that MRI was less bothersome than prostate biopsy *[54]*. We believe that in Australia using mpMRI to determine if biopsy is indicated is more acceptable than proceeding to invasive biopsy on the basis of elevated PSA levels alone.

Feasibility

We believe that the intervention is feasible, as metropolitan areas in Australia have excellent access to appropriate mpMRI services. Regional and remote individuals may be required to travel long distances, however, as mpMRI is not considered an emergency procedure this is not an important concern.

The use of PSA density is highly feasible as it is calculated using the PSA level and prostate volume which is reported by the mpMRI, i.e. no additional testing is required.

mpMRI and PSAD measurement are less burdensome to patients than an invasive biopsy which involves hospital admission and associated risks.

Rationale

For this recommendation, several protocols were examined to determine if mpMRI could be used to triage men with no history of prostate cancer and an elevated PSA for prostate biopsy. Overall, the evidence suggested that avoiding biopsy for those with a PI-RADS of 1 or 2 or a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL offered the largest reduction (around 50%) in unnecessary biopsies (benefits) for a trivial increase in undetected

clinically significant disease (harms). For those who do not have immediate biopsy, any harms can be mitigated through appropriate monitoring with PSA testing and/or mpMRI. Therefore, we concluded that the large benefit of mpMRI triage in reducing the number of unnecessary biopsies performed outweighs the small risk of initially undetected significant cancer.

The studies examined all related to diagnostic accuracy and not clinical outcomes. We did not find evidence for the effect of mpMRI triage on clinical outcomes (prostate cancer mortality, overall mortality and metastatic disease) and as a result the overall certainty of the evidence was downgraded. This remains an area of focus as evidence becomes available in the future.

No areas of major debate about the evidence and this recommendation were identified. This recommendation was reached with full consensus.

Clinical question/ PICO

Population: Men with no history of prostate cancer and elevated PSA levels (biopsy naïve)
Intervention: mpMRI triage to biopsy
Comparator: No mpMRI triage to biopsy – all men with elevated PSA levels undergo biopsy

Summary

Five studies were identified that investigated the use of mpMRI alone to triage men with elevated PSA levels to prostate biopsy *[48]*, *[49]*, *[50]*, *[51]*, *[52]*, *[53]*. Findings from one of the studies, the PROMIS study, were published in 2017 *[51]* and 2020 *[52]*. A meta-analysis of the results from these studies showed that mpMRI could be used to triage men to biopsy. Men with mpMRI PI-RADS 1 or 2 lesions are unlikely to need a biopsy as the number of clinically significant cancers undetected is not clinically important (< 50/1000). If men with PI-RADS 1, 2 or 3 lesions are not biopsied, there is the possibility that a small (50 -100/1000) but clinically important number of clinically significant cancers may not be detected. Consequently, biopsy is required for men with PI-RADS 4 and 5 lesions and for at least some men with PI-RADS 3 lesions.

If the prevalence of clinically insignificant (ISUP grade 1) cancer is 20%, it is estimated that 63.5% (127/200) of clinically insignificant cancer will not be detected if men with a PI-RADS 1, 2 or 3 lesions are not biopsied, and 32% (64/200) of clinically insignificant cancer will not be detected if men with a PI-RADS 1 or 2 lesions are not biopsied.

The certainty of evidence was moderate or low. All five studies had a high risk of selection bias as in each of these studies it was considered likely that not all men with an elevated PSA were offered mpMRI. In addition, there were serious concerns as to whether the number of clinically significant cancers undetected is small if men with PI-RADS 1, 2 or 3 lesions do not undergo biopsy as the 95% confidence interval included clinically unimportant differences.

Note: the evidence in this PICO informed conditional recommendations 6.2 and 6.3.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 23 (95%CI:18, 28) based on a summary sensitivity of 0.887 (0.86, 0.91).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2 the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.
Clinically significant (ISUP	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected		**Low** Downgraded by two levels due to	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical		ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 51 (95%CI:46, 58) based on a summary sensitivity of 0.744 (0.71, 0.77).		serious concerns re potential selection bias and imprecision	≥ 2 prostate cancers maybe small but clinically important.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 339 (95%CI:312, 368) based on a summary specificity of 0.424 (0.39, 0.46)		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2 the number of unnecessary biopsies avoided is likely moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 585 (95%CI:560, 608) based on a summary specificity of 0.731 (0.70, 0.76)		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-3 the number of unnecessary biopsies avoided is likely large.
ISUP Grade ≥ 3 prostate cancer not detected where the prevalence of ISUP Grade ≥ 3 disease is 20% 8 Critical	Based on data from 1,859 participants in 5 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of undetected ISUP Grade ≥ 3 prostate cancers in a population of 1000 men with elevated PSA levels is 10 (95%CI:6, 16) based on a summary sensitivity of 0.949 (0.92, 0.97).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2 the number of undetected ISUP Grade ≥ 3 prostate cancers is likely clinically unimportant.
ISUP Grade ≥ 3 prostate cancer not detected where the prevalence of ISUP Grade ≥ 3	Based on data from 1,696 participants in 4 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected ISUP Grade ≥ 3 prostate cancers in a population of 1000 men with elevated PSA levels is 21 (95%CI:14, 30) based on a summary sensitivity of 0.897 (0.85, 0.93).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade ≥ 3 prostate cancers is likely clinically unimportant.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
disease is 20% 8 Critical					
ISUP Grade 1 prostate cancer not detected where the prevalence of ISUP Grade 1 disease is 20% 7 Critical	Based on data from 1,546 participants in 3 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of undetected ISUP Grade 1 prostate cancers in a population of 1000 men with elevated PSA levels is 64 (95%CI:54, 76) based on a summary sensitivity of 0.675 (0.62, 0.73).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2 the number of undetected ISUP Grade 1 prostate cancers is likely clinically unimportant.
ISUP Grade 1 prostate cancer not detected where the prevalence of ISUP Grade 1 disease is 20% 7 Critical	Based on data from 1,383 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected ISUP Grade 1 prostate cancers in a population of 1000 men with elevated PSA levels is 127 (95%CI:114, 138) based on a summary sensitivity of 0.366 (0.31, 0.43).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade 1 prostate cancers is likely small but clinically important.

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Clinical question/ PICO

Population: Men with no history of prostate cancer with elevated PSA levels (biopsy naïve)
Intervention: mpMRI triage to biopsy
Comparator: No mpMRI triage to biopsy – all men with elevated PSA levels undergo biopsy

Summary

This PICO examined the effect of mpMRI triage on patient relevant outcomes, specifically all-cause mortality, prostate cancer mortality or metastases as well as cancer detection outcomes. Systematic searches of the literature did not identify any randomised controlled trial evidence for this PICO.

This question remains an area of interest. Searches of clinical trial registries and literature searches identified three potentially relevant ongoing trials. Research in this area will be monitored and the Guidelines revised as new relevant data becomes available.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy	**Certainty of the evidence** (Quality of evidence)
All cause mortality, prostate cancer mortality or metastasis		No relevant randomised controlled trials identified.		
ISUP grade ≥ 2 prostate cancer detection, or ISUP grade 1 prostate cancer detection, or biopsy rates		No relevant randomised controlled trials identified.		

Clinical question/ PICO

Population: Men with no history of prostate cancer and elevated PSA levels who are biopsy naïve and mpMRI negative and do not undergo biopsy.
Intervention: Follow-up protocol
Comparator: Another follow-up protocol or no specific follow-up

Summary

This PICO examined the effect of follow-up protocols to detect clinically significant prostate cancer in men who are MRI negative and did not undergo biopsy. Systematic searches of the literature did not identify any RCT evidence for the effect of different the different follow-up protocols for these men on disease outcomes, specifically all-cause mortality, prostate cancer mortality or metastasis.

This question remains an area of interest. Searches of clinical trial registries and literature searches identified three potentially relevant ongoing trials. Research in this area will be monitored and the Guidelines revised as new relevant data becomes available.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** Another follow-up protocol or no specific follow-up	**Intervention** Follow-up protocol	**Certainty of the evidence** (Quality of evidence)
All cause mortality, prostate cancer mortality or metastasis		No suitable studies found		

Clinical question/ PICO

Population: Men with no history of prostate cancer with elevated PSA levels (biopsy naïve)
Intervention: Triage to biopsy using mpMRI with or without PSA density using a threshold of 0.15 µg/L/mL
Comparator: No mpMRI triage to biopsy – all men with elevated PSA levels undergo biopsy

Summary

This PICO compares the diagnostic accuracy of mpMRI plus PSA density with that of mpMRI alone for the detection of clinically significant prostate cancer in biopsy naïve men to determine whether PSA density might be used to distinguish a subgroup of individuals with an equivocal PI-RADS 3 lesion who might not require an immediate biopsy.

Two studies were found that met the criteria for inclusion in our systematic review *[48]*, *[49]*. Meta-analyses of their results enabled the comparison of outcomes for a range of different triage protocols when compared with no triage within the same cohorts. For individuals with a PI-RADS less than 4, protocols offering biopsies only to those with a PSA density ≥ 0.15 µg/L/mL are estimated to result in a clinically unimportant (< 50) undetected clinically significant (ISUP Grade ≥ 2) cancers in a population of 1000 men with elevated PSA levels. The largest number of unnecessary biopsies are avoided if only those with mpMRI PI-RADS 3 and a PSA density ≥ 0.15 µg/L/mL undergo biopsy. The certainty of the evidence for this protocol was moderate due to concerns regarding selection bias.

More information can be found in the Technical Report.

Note: the evidence in this PICO informed conditional recommendations 6.2 and 6.3.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy with/without PSAD ≥ 0.15 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2** who have a **PSAD < 0.15 µg/L/mL** the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 11 (95%CI: 8, 16) based on a summary sensitivity of 0.947 (0.92, 0.96).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2 who have a PSAD < 0.15 µg/L/mL the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy with/without PSAD ≥ 0.15 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
significant disease is 20% 8 Critical					
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.15 µg/L/mL** the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 23 (95%CI: 18, 30) based on a summary sensitivity of 0.884 (0.85, 0.91).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS 1-3 who have a PSAD < 0.15 µg/L/mL the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2**, the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 23 (95%CI:18, 30) based on a summary sensitivity of 0.884 (0.85, 0.91).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias	If do not biopsy men with a PI-RADS of 1-2, the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.15 µg/L/mL** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 36 (95%CI:28, 44) based on a summary sensitivity of 0.822 (0.78, 0.86).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL, the number of undetected ISUP Grade ≥ 2 prostate cancers may be clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated		**Low** Downgraded by two levels due to serious concerns re	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade ≥ 2 prostate cancers may be clinically unimportant.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy with/without PSAD ≥ 0.15 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
not detected where the prevalence of clinically significant disease is 20% 8 Critical		PSA levels is 47 (95%CI:40, 56) based on a summary sensitivity of 0.766 (0.72, 0.80).		potential selection bias and imprecision.	
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2** who have a **PSAD < 0.15 µg/L/mL** the number of unnecessary biopsies avoided in a population of 1000 asymptomatic individuals with elevated PSA levels is 226 (95%CI: 200, 256) based on a summary specificity of 0.283 (0.25, 0.32).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2 who have a PSAD < 0.15 µg/L/mL the number of unnecessary biopsies avoided is likely moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.15 µg/L/mL** the number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 373 (95%CI: 336, 408) based on a summary specificity of 0.466 (0.42, 0.51).		**Low** Downgraded by two levels due to serious concerns re potential selection bias and imprecision.	If do not biopsy men with a PI-RADS 1-3 who have a PSAD < 0.15 µg/L/mL the number of unnecessary biopsies avoided may be moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 354 (95%CI:320, 392) based on a summary specificity of 0.443 (0.40, 0.49).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2 the number of unnecessary biopsies avoided is likely moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20%	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.15 µg/L/mL** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 500 (95%CI:464, 536) based on a summary specificity of 0.625 (0.58, 0.67).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL, the number of unnecessary biopsies avoided is likely large.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy	**Intervention** mpMRI triage to biopsy with/without PSAD ≥ 0.15 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
7 Critical					
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 947 participants in 2 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 566 (95%CI:536, 592) based on a summary specificity of 0.707 (0.67, 0.74)		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-3 the number of unnecessary biopsies avoided is likely large.

Clinical question/ PICO

Population: Men with no history of prostate cancer with elevated PSA levels (biopsy naïve)
Intervention: Triage to biopsy using mpMRI with or without PSA density using a threshold of 0.15 or 0.20 µg/L/mL
Comparator: No mpMRI triage to biopsy – all men with elevated PSA levels undergo biopsy

Summary

For this PICO one study was found that compared diagnostic accuracy outcomes using mpMRI and PSAD thresholds of 0.15 and 0.20 µg/L/mL to triage men to biopsy *[48]*. In this study if men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSA density < 0.15 µg/L/mL were not biopsied the number of undetected clinically significant cancers was likely clinically unimportant (< 50/1000) whereas if a PSA density threshold of 0.20 µg/L/mL was used the number of undetected clinically significant cancers was higher and it was less certain whether the number would be clinically unimportant.

More information can be found in the Technical Report.

Note: the evidence in this PICO informed conditional recommendations 6.2 and 6.3.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy with/without PSAD 0.15 or 0.20 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.15 µg/L/mL** the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 25 (95%CI: 18, 32) based on a summary sensitivity of 0.875 (0.84, 0.91).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-3 who have a PSAD < 0.15 µg/L/mL the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy with/without PSAD 0.15 or 0.20 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
disease is 20% 8 Critical					
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.20 µg/L/mL** the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 34 (95%CI: 26, 42) based on a summary sensitivity of 0.829 (0.79, 0.87).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS 1-3 who have a PSAD < 0.20 µg/L/mL the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.15 µg/L/mL** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 38 (95%CI:30, 46) based on a summary sensitivity of 0.811 (0.77, 0.85).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL, the number of undetected ISUP Grade ≥ 2 prostate cancers is likely clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 20% 8 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.20 µg/L/mL** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated PSA levels is 42 (95%CI:34, 52) based on a summary sensitivity of 0.788 (0.74, 0.83).		**Low** Downgraded by two levels due to serious concerns re potential selection bias and imprecision.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.20 µg/L/mL, the number of undetected ISUP Grade ≥ 2 prostate cancers may be clinically unimportant.
Clinically significant (ISUP Grade ≥ 2) prostate cancer	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 men with elevated		**Low** Downgraded by two levels due to serious concerns re potential selection	If do not biopsy men with a PI-RADS of 1-3 the number of undetected ISUP Grade ≥ 2 prostate cancers may be clinically unimportant.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy with/without PSAD 0.15 or 0.20 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
not detected where the prevalence of clinically significant disease is 20% 8 Critical		PSA levels is 48 (95%CI:40, 58) based on a summary sensitivity of 0.758 (0.71, 0.83).		bias and imprecision.	
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.15 µg/L/mL** the number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 376 (95%CI: 336, 416) based on a summary specificity of 0.470 (0.42, 0.52).		**Low** Downgraded by two levels due to serious concerns re potential selection bias and imprecision.	If do not biopsy men with a PI-RADS of 1-3 who have a PSAD < 0.15 µg/L/mL the number of unnecessary biopsies avoided may be moderate.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** who have a **PSAD < 0.20 µg/L/mL** the number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 482 (95%CI: 440, 520) based on a summary specificity of 0.602 (0.55, 0.65).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS 1-3 who have a PSAD < 0.20 µg/L/mL the number of unnecessary biopsies avoided is likely large.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-2** or men with a **PI-RADS of 3 and a PSAD < 0.15 µg/L/mL** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 505 (95%CI:464, 544) based on a summary specificity of 0.631 (0.58, 0.68).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2 , or men with a PI-RADS of 3 and a PSAD < 0.15 µg/L/mL, the number of unnecessary biopsies avoided is likely large.
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20%	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-2,** or men with a **PI-RADS of 3 and a PSAD < 0.20 µg/L/mL** the estimated number of unnecessary biopsies avoided in a population of 1000 men with elevated PSA levels is 542 (95%CI:504, 576) based on a summary specificity of 0.677 (0.63, 0.72).		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-2, or men with a PI-RADS of 3 and a PSAD < 0.20 µg/L/mL, the number of unnecessary biopsies avoided is likely large.

Outcome Timeframe	**Study results and measurements**	**Comparator** No mpMRI triage to biopsy – all men with elevated PSA levels un	**Intervention** mpMRI triage to biopsy with/without PSAD 0.15 or 0.20 µg/L/mL	**Certainty of the evidence** (Quality of evidence)	**Summary**
7 Critical					
Unnecessary biopsies avoided where the prevalence of clinically significant disease is 20% 7 Critical	Based on data from 807 participants in 1 studies.	If do not biopsy men with a **PI-RADS of 1-3** the estimated number of unnecessary biopsies avoided in a population of 1000 asymptomatic individuals with elevated PSA levels is 566 (95%CI:528, 600) based on a summary specificity of 0.708 (0.66, 0.75)		**Moderate** Downgraded by one level due to serious concerns re potential selection bias.	If do not biopsy men with a PI-RADS of 1-3 the number of unnecessary biopsies avoided is likely large.

Consensus recommendation

6.4 We propose that for males with elevated PSA who do not require biopsy based on the 6.3 Conditional recommendation subsequent management will vary according to their degree of clinical risk. This should include discussion of individual preferences.

A repeat PSA and specialist review should guide subsequent management. For males with additional risk factors for cancer and those more concerned about missing a diagnosis, further management options may include a repeat PSA within 6 months, a prostate specific membrane antigen positron emission tomography with computer tomography (PSMA PET/CT) scan, or undergoing a transperineal systematic biopsy.

Refer 7.3 Good practice statement

Review by 2030, subject to emerging evidence

Rationale

Men with elevated PSA levels who do not undergo biopsy as a result of mpMRI triage will need to be followed up as some will have undetected clinically significant disease (See evidence for conditional recommendations 6.2 and 6.3). Systematic searches of the literature did not identify any RCT evidence for the effect of different follow-up protocols for these men on disease outcomes, specifically all-cause mortality, prostate cancer mortality or metastasis. In the absence of any evidence a consensus-based recommendation based on expert opinion and consumer input is provided.

Clinical question/ PICO

Population: Men with no history of prostate cancer and elevated PSA levels who are biopsy naïve and mpMRI negative and do not undergo biopsy.

Intervention: Follow-up protocol

Comparator: Another follow-up protocol or no specific follow-up

Summary

This PICO examined the effect of follow-up protocols to detect clinically significant prostate cancer in men who are MRI negative and did not undergo biopsy. Systematic searches of the literature did not identify any RCT evidence for the effect of different the different follow-up protocols for these men on disease outcomes, specifically all-cause mortality, prostate cancer mortality or metastasis.

This question remains an area of interest. Searches of clinical trial registries and literature searches identified three potentially relevant ongoing trials. Research in this area will be monitored and the Guidelines revised as new relevant data becomes available.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** Another follow-up protocol or no specific follow-up	**Intervention** Follow-up protocol	**Certainty of the evidence** (Quality of evidence)
All cause mortality, prostate cancer mortality or metastasis		No suitable studies found		

Good practice statement

6.5 Males who cannot access or have an mpMRI may be offered a systematic transperineal biopsy or PSMA PET/CT.

mpMRI acquisition should include T2-weighted, diffusion-weighted and dynamic contrast-enhanced series.

mpMRI reports should include the PI-RADS score for each suspicious lesion, the prostate volume, and the PSAD calculation.

The PSAD calculation should be based on the most recent PSA result prior to the mpMRI.

Review by 2030, subject to emerging evidence

7. Specialist setting - Prostate biopsy

Clinical Questions

For biopsy naïve men with a PI-RADS 4 or 5 lesion on mpMRI are targeted biopsies alone acceptable/reasonable/adequate? (Clinical question 8)

For biopsy naïve men with a PI-RADS 3 lesion on mpMRI are targeted biopsies alone acceptable/reasonable/adequate? (Clinical question 9)

Background

Prostate biopsy remains the only way to definitively diagnose prostate cancer. It is an invasive surgical procedure used to collect samples of prostate tissue. Like all surgical procedures, it comes with potential risks including infection, bleeding and adverse reactions to anaesthesia.

Previously, the decision to perform a prostate biopsy was made on the basis of PSA testing. In recent years, clinical practice has increasingly used multiparametric magnetic resonance imaging (mpMRI) in addition to PSA testing. 5. Primary health care setting - PSA testing of these Guidelines examined the use of mpMRI to determine which patients should be offered a biopsy. In this section of the Guidelines, we examined the use of targeted and systematic biopsies for patients with mpMRI PI-RADS 3 and PI-RADS 4-5 lesions for the detection of clinically significant prostate cancer (ISUP Grade ≥ 2).

Conditional recommendation

7.1 We suggest that for patients with a Prostate Imaging Reporting and Data System (PI-RADS) 4-5 lesion, multiparametric magnetic resonance imaging (mpMRI) targeted plus systematic biopsies should be undertaken.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Important harms

Benefits/desirable effects

No evidence was found for the benefits of eliminating a systematic biopsy when using a transperineal approach.

Two relevant RCTs reported hospitalisations following transrectal biopsies. Neither reported a clinically important decrease in serious biopsy complications. Based on a predetermined minimal clinical important difference of 50 hospital admissions within 30 days of biopsy/1000, the difference in the number of hospitalisations within 30 days of biopsy was **trivial (clinically unimportant)** if MRI-targeted biopsies plus a 12-core systematic biopsy rather than a 20-core systematic biopsy is undertaken *[155]* or if MRI-targeted biopsies only rather than MRI-targeted biopsies plus a systematic biopsy is undertaken *[211]*.

No evidence was found for an impact on urinary retention resulting in hospitalisation. One of the RCTs *[155]* considered hospital admissions after biopsy; in this trial the only admissions due to biopsy complications were for post biopsy fever which is less of a concern if a transperineal approach is used. The other RCT *[211]* considered hospital admissions for any cause in the 30 days following biopsy. This study reported 5 hospital admissions none of which were due to urinary retention.

No evidence was found for the outcomes of ISUP 1 detection or longer-term erectile dysfunction ≥ 1-year post-biopsy.

Harms/ undesirable effects

All three fully paired studies providing evidence of harms of eliminating a systematic biopsy used a transperineal approach *[48][50][53]*. They reported clinically significant cancer detection for MRI-targeted biopsies alone and for MRI-targeted biopsies plus a ≥ 20-core systematic biopsy for men with mpMRI score 4-5 lesions. For the targeted biopsies two of the three studies *[48]*, *[50]* used a minimum of 2 cores per lesion and the third *[53]*, took a median of 4 cores per lesion. For the systematic biopsies, two of the three studies *[48]*, *[53]* used the Ginsberg protocol whilst the other study *[50]* used a saturation biopsy.

Each of these studies indicated that the detection of clinically significant disease was reduced if only targeted biopsies were undertaken.

If the prevalence of ISUP Grade ≥ 2 disease is 70% in this population, using a predetermined minimal clinically important difference of 50 undetected ISUP Grade ≥ 2 prostate cancer/1000 and thresholds of 100/1000 and 200/1000 for moderate and large effects, **a clinically important (large)** number of clinically significant prostate cancers would not be detected if a ≥ 20-core systematic biopsy is not undertaken in addition to MRI-targeted biopsies.

If the prevalence of ISUP Grade ≥ 3 disease is 30% in this population, using a minimal clinically important difference of 35 undetected ISUP Grade ≥ 3 prostate cancer/1000 and thresholds of 70/1000 and 140/1000 for moderate and large effects, **a clinically important (large)** number of ISUP grade ≥ 3 prostate cancers will not be detected if a ≥ 20-core systematic biopsy is not undertaken in addition to MRI-targeted biopsies.

We found no evidence as to the effects on the detection of clinically important prostate cancer of reducing the number of systematic biopsy cores from ≥20 to 12-20 when performing systematic biopsy plus MRI-targeted biopsies.

No evidence was found as to the impacts of not undertaking a ≥ 20-core systematic biopsy in addition to MRI-targeted biopsies on long-term patient relevant outcomes such as metastases and prostate cancer mortality.

Balance of benefits and harms/ desirable and undesirable effects

For men with mpMRI score 4-5 lesions if a ≥20-core systematic biopsy is not undertaken in addition to MRI-targeted biopsies there are important potential harms (reduced detection of clinically significant prostate cancer), whereas, where evidence was available, the benefits are trivial.

The important harms of not diagnosing clinically significant disease on biopsy in this population outweighs any possible benefits which are currently either uncertain and trivial (reduction in hospitalisations post biopsy for sepsis or fever) or unknown (reduction ISUP Grade 1 diagnoses, post biopsy urinary retention requiring hospitalisation and long-term erectile dysfunction following biopsy).

Certainty of the evidence

Moderate

The evidence for the benefits of not undertaking a systematic biopsy as well as MRI-targeted biopsies is either not available or of low or very low certainty. The scant evidence for the benefits of not undertaking a systematic biopsy is rated low or very low due to indirectness as in both included trials the comparisons and outcomes assessed were not directly relevant to the PICO and a transrectal rather than a transperineal approach was used which is less relevant to the Australian context. There were also serious concerns regarding imprecision for one of the two trials *[155]*.

In contrast the certainty of the evidence for the undesirable effects/harms of eliminating a systematic biopsy and consequently for continuing to include a systematic biopsy is high. The evidence of harms is based on the impact on the detection of clinically significant cancer, not subsequent long-term patient relevant outcomes such as rates of metastases and prostate cancer deaths for which there is no evidence.

As a result, the overall certainty of the evidence for undesirable effects/harms of undertaking only MRI-targeted biopsies and consequently for continuing to include a systematic biopsy, was rated moderate.

Values and preferences

No substantial variability expected

No research evidence

In the Australian context in which most prostate biopsies are undertaken under general anaesthesia using a transperineal approach most men would prefer a definitive diagnosis and would value avoiding the risk of missed clinically significant prostate cancer over any uncertain trivial or hypothetical risks of serious complications and ISUP 1 diagnoses associated with undertaking a systematic biopsy as well as a targeted biopsy.

Resources and other considerations

No important issues with the recommended alternative

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

No research evidence.

In the Australian context in which most prostate biopsies are undertaken under general anaesthesia a single biopsy procedure in which both targeted biopsy cores and systematic biopsy cores are taken is common practice and acceptable to patients, their caregivers and health providers.

Feasibility

No research evidence.

In the Australian context in which most prostate biopsies are undertaken under general anaesthesia there are no barriers to a single biopsy procedure in which both targeted biopsy cores and systematic biopsy cores are taken.

In contrast, eliminating a systematic biopsy and undertaking a targeted biopsy followed by a second biopsy if a clinical suspicion of prostate cancer remains on follow-up, would be more burdensome to a significant proportion of those patients with a negative targeted biopsy and the healthcare system.

Rationale

For this recommendation, several protocols were examined to determine the best biopsy procedure for patients with mpMRI PI-RADS 4-5 lesions for the detection of clinically significant prostate cancer (ISUP Grade ≥ 2).

Overall, the evidence suggested that for patients with PI-RADS 4-5 lesions, there are important harms of not diagnosing clinically significant disease if systematic biopsy is not undertaken in addition to MRI-targeted biopsy.

The important harms of not diagnosing clinically significant disease on biopsy in this population outweighs any possible benefits which are currently either uncertain or unknown.

No areas of major debate about the evidence and this recommendation were identified. This recommendation was reached with full consensus.

Clinical question/ PICO

Population: Males with mpMRI PI-RADS 4 or 5 lesions (biopsy naïve)
Intervention: MRI-targeted biopsy
Comparator: MRI-targeted biopsy plus ≥ 20-core systematic biopsy

Summary

Three studies were identified that investigated the use of MRI-targeted biopsy alone for men with PI-RADS 4 or 5 lesions with elevated PSA levels undergoing initial prostate biopsy *[48]*, *[50]*, *[53]*. A meta-analysis of the results from these studies showed that a clinically important number of clinically significant (ISUP grade ≥ 2) prostate cancers (>50/1000) and ISUP grade ≥ 3 prostate cancers (>35/1000) will not be detected if a ≥ 20 core systematic biopsy is not undertaken in addition to a targeted biopsy if the prevalence of clinically significant prostate cancer is 70%. The certainty of evidence was high. No evidence was found for the detection of ISUP grade 1 prostate cancer.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** MRI-targeted biopsy plus ≥ 20-core systematic biopsy	**Intervention** MRI-targeted biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 70% 9 Critical	Based on data from 559 participants in 3 studies.	For men with a mpMRI score 4-5 lesion if undertake only targeted biopsies the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 is 252 (95%CI: 98, 434) based on a summary relative sensitivity of 0.64 (95%CI: 0.38, 0.86).		**High**	For biopsy-naïve men with a mpMRI score 4-5 lesion a clinically important number of clinically significant cancers will not be detected if a ≥ 20 core systematic biopsy is not undertaken in addition to a targeted biopsy.
ISUP Grade ≥ 3 prostate cancer not detected where the prevalence of clinically significant disease is 30% 8 Critical	Based on data from 111 participants in 1 studies.	For men with a mpMRI score 4-5 lesion if undertake only targeted biopsies the number of undetected ISUP Grade ≥ 3 prostate cancers in a population of 1000 is 174 (95%CI: 120, 225) based on a summary relative sensitivity of 0.42 (0.25, 0.60)		**High**	For biopsy-naïve men with a mpMRI PI-RADS 4-5 lesion a clinically important 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

Outcome Timeframe	**Study results and measurements**	**Comparator** MRI-targeted biopsy plus ≥ 20-core systematic biopsy	**Intervention** MRI-targeted biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
ISUP Grade 1 prostate cancer detection		No relevant studies identified. More information can be found in the Technical Report.			

References

48. Hansen NL, Barrett T, Kesch C, Pepdjonovic L, Bonekamp D, O'Sullivan R, et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer. BJU international 2018;122(1):40-49 Pubmed Journal

50. Mortezavi A, Märzendorfer O, Donati OF, Rizzi G, Rupp NJ, Wettstein MS, 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. The Journal of urology 2018;200(2):309-318 Pubmed Journal

53. Bonekamp D, Schelb P, Wiesenfarth M, Kuder TA, Deister F, Stenzinger A, et al. Histopathological to multiparametric MRI spatial mapping of extended systematic sextant and MR/TRUS-fusion-targeted biopsy of the prostate. European radiology 2019;29(4):1820-1830 Pubmed Journal

Clinical question/ PICO

Population: Males with mpMRI PI-RADS 4 or 5 lesions (biopsy naïve)
Intervention: MRI-targeted biopsy plus 12-core systematic biopsy
Comparator: MRI-targeted biopsy plus ≥ 20-core systematic biopsy

Summary

Systematic searches of the literature did not identify any relevant studies reporting on the detection of clinically significant and insignificant prostate cancers if the number of systematic biopsy cores are reduced from ≥20 to 12-20 when performing systematic biopsy plus MRI-targeted biopsies for men with mpMRI PI-RADS 4-5.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** MRI-targeted biopsy plus ≥ 20-core systematic biopsy	**Intervention** MRI-targeted biopsy plus 12-core systematic biopsy	**Certainty of the evidence** (Quality of evidence)
Clinically significant (ISUP Grade ≥ 2) prostate cancer detection		No relevant studies identified.		

Outcome Timeframe	**Study results and measurements**	**Comparator** MRI-targeted biopsy plus ≥ 20-core systematic biopsy	**Intervention** MRI-targeted biopsy plus 12-core systematic biopsy	**Certainty of the evidence** (Quality of evidence)
ISUP Grade ≥ 3 prostate cancer detection		No relevant studies identified.		
ISUP Grade 1 prostate cancer detection		No relevant studies identified.		

Clinical question/ PICO

Population: Males with undergoing prostate biopsy
Intervention: MRI-targeted biopsy alone
Comparator: MRI-targeted biopsy plus 12-core systematic biopsy

Summary

Based on evidence from one randomised controlled trial that used a transrectal biopsy approach, the difference in the number of hospitalisations within 30 days of biopsy was clinically unimportant (<50/1000) if MRI-targeted biopsies only rather than MRI-targeted biopsies plus a systematic biopsy was undertaken *[211]*. The certainty of evidence was low due to very serious concerns regarding indirectness. No evidence was found for the outcome of longer-term erectile dysfunction ≥ 1-year post-biopsy.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** MRI-targeted biopsy alone	**Certainty of the evidence** (Quality of evidence)	**Summary**
Hospitalisation post-biopsy 30 days 9 Critical	Relative risk 0.29 (CI 95% 0.03 — 2.57) Based on data from 649 participants in 1 studies.	12 per 1000 Difference:	3 per 1000 **8.5 fewer per 1000** (CI 95% 11 fewer — 18 more)	**Low** Downgraded by two levels due to very serious concerns re: indirectness	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.
Erectile dysfunction post-biopsy ≥ 1 year		No relevant studies identified.			

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** MRI-targeted biopsy alone	**Certainty of the evidence** (Quality of evidence)	**Summary**

References

211. Hugosson J, Månsson M, Wallström J, Axcrona U, Carlsson SV, Egevad L, et al. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. New England Journal of Medicine 2022;387(23):2126-2137

Clinical question/ PICO

Population: Males undergoing prostate biopsy
Intervention: MRI-targeted biopsy plus 12-core systematic biopsy
Comparator: ≥20-core systematic biopsy

Summary

Based on evidence from one randomised controlled trial that used a transrectal biopsy approach, the difference in the number of hospitalisations post-biopsy was clinically unimportant (<50/1000) if MRI-targeted biopsies plus a 12-core systematic biopsy, rather than a 20-core systematic biopsy alone was undertaken *[155]*. [The certainty of evidence was very low due to serious concerns regarding imprecision and indirectness. No evidence was found for the outcome of longer-term erectile dysfunction ≥ 1-year post-biopsy. More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention**	**Certainty of the evidence** (Quality of evidence)	**Summary**
Hospitalisation post-biopsy No timeframe 9 Critical	Relative risk 0.98 (CI 95% 0.06 — 15.28) Based on data from 105 participants in 1 studies.	**19** per 1000 Difference:	**19** per 1000 **0.2 fewer per 1000** (CI 95% 18 fewer — 274 more)	**Very low** Downgraded by three levels due to extremely serious concerns re: imprecision and serious concerns re: indirectness	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.
Erectile dysfunction post-biopsy ≥ 1 year		No relevant studies identified.			

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention**	**Certainty of the evidence** (Quality of evidence)	**Summary**

References

155. Dadpour M, Soltani AM, Ghafoori M, Basiri A, Borumandnia N, Nayebzade A, et al. Ultrasound/MRI-targeted biopsy versus saturated trans-rectal ultrasound guided biopsy of prostate in patients with primary negative conventional biopsy and still elevated PSA: a prospective randomized clinical trial. American Journal of Clinical and Experimental Urology 2023;11(4):312

Conditional recommendation

7.2 We suggest that for patients with a PI-RADS 3 lesion who require biopsy, mpMRI-targeted biopsies plus systematic biopsies should be undertaken.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms Important harms

Benefits/desirable effects

No evidence was found for the benefits of eliminating a systematic biopsy when using a transperineal approach.

Two relevant RCTs reported hospitalisations following transrectal biopsies. Neither reported a clinically important decrease in serious biopsy complications. Based on a predetermined minimal clinical important difference of 50 hospital admissions within 30 days of biopsy/1000, the difference in the number of hospitalisations within 30 days of biopsy was **trivial (clinically unimportant)** if MRI-targeted biopsies plus a 12-core systematic biopsy rather than a 20-core systematic biopsy is undertaken *[155]* or if MRI-targeted biopsies only rather than MRI-targeted biopsies plus a systematic biopsy is undertaken *[211]*.

No evidence was found for an impact on urinary retention resulting in hospitalisation. One of the RCTs *[155]* considered hospital admissions after biopsy; in this trial the only admissions due to biopsy complications were for post biopsy fever which is less of a concern if a transperineal approach is used. The other RCT *[211]* considered hospital admissions for any cause in the 30 days following biopsy. This study reported 5 hospital admissions none of which were due to urinary retention.

No evidence was found for the outcomes of ISUP 1 detection or longer-term erectile dysfunction ≥ 1-year post-biopsy.

Harms/undesirable effects

All three fully paired studies studies providing evidence of harms of eliminating a systematic biopsy used a transperineal approach *[48]*, *[50]*, *[53]*. They reported clinically significant cancer detection for MRI- targeted biopsies alone and for MRI-targeted biopsies plus a ≥ 20-core systematic biopsy for men with mpMRI score 3 lesions. For the targeted biopsies two of the three studies *[48]*, *[50]* used a minimum of 2 cores per lesion and the third *[53]* took a median of 4 cores per lesion. For the systematic biopsies, two of the three studies *[48]*, *[53]* used the Ginsberg protocol whilst the other study *[50]* used a saturation biopsy.

Each of these studies indicated that the detection of clinically significant disease was reduced if only targeted biopsies were undertaken.

If the prevalence of ISUP Grade ≥ 2 disease is 30% in this population, using a predetermined minimal clinically important difference of 50 undetected ISUP Grade ≥ 2 prostate cancer/1000 and thresholds of 100/1000 and 200/1000 for moderate and large effects, **a clinically important (moderate)** number of clinically significant prostate cancers would not be detected if a ≥ 20-core systematic biopsy is not undertaken in addition to MRI-targeted biopsies.

We found no evidence as to the effects on the detection of clinically important prostate cancer of reducing the number of systematic biopsy cores from ≥20 to 12-20 when performing systematic biopsy plus MRI-targeted biopsies.

No evidence was found as to the impacts of not undertaking a ≥ 20-core systematic biopsy in addition to MRI-targeted biopsies on the detection of ISUP Grade ≥ 3 disease or long-term patient relevant outcomes such as metastases and prostate cancer mortality.

Balance of benefits and harms/desirable and undesirable effects

For men with mpMRI score 3 lesions if a ≥20-core systematic biopsy is not undertaken in addition to MRI-targeted biopsies there are important potential harms (reduced detection of clinically significant prostate cancer) whereas, where evidence was available, the benefits are trivial.

The important harms of not diagnosing clinically significant disease on biopsy in this population outweighs any possible benefits which are currently either uncertain and trivial (reduction in hospitalisations post biopsy for sepsis or fever) or unknown (reduction ISUP Grade 1 diagnoses, post biopsy urinary retention requiring hospitalisation and long-term erectile dysfunction following biopsy).

Certainty of the evidence

Moderate

The evidence for the benefits of not undertaking a systematic biopsy as well as MRI-targeted biopsies is either not available or of low or very low certainty. The scant evidence for the benefits of not undertaking a systematic biopsy is rated low or very low due to indirectness as in both included trials the comparisons and outcomes assessed were not directly relevant to the PICO and a transrectal rather than a transperineal approach was used which is less relevant to the Australian context. There were also serious concerns regarding imprecision for one of the two trials *[155]*. In contrast the certainty of the evidence for the undesirable effects/harms of eliminating a systematic biopsy and consequently for continuing to include a systematic biopsy is high.

The evidence of harms is based on the impact on the detection of clinically significant cancer, not subsequent long-term patient relevant outcomes such as rates of metastases and prostate cancer deaths for which there is no evidence.

As a result, the overall certainty of the evidence for undesirable effects/harms of undertaking only MRI-targeted biopsies and consequently for continuing to include a systematic biopsy, was rated moderate.

Values and preferences

No substantial variability expected

No research evidence.

In the Australian context in which most prostate biopsies are undertaken under general anaesthesia using a transperineal approach most men would prefer a definitive diagnosis and would value avoiding the risk of missed clinically significant prostate cancer over any uncertain trivial or hypothetical risks of serious complications and ISUP 1 diagnoses associated with undertaking a systematic biopsy as well as a targeted biopsy.

Resources and other considerations

No important issues with the recommended alternative

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability

No research evidence

In the Australian context in which most prostate biopsies are undertaken under general anaesthesia a single biopsy procedure in which both targeted biopsy cores and systematic biopsy cores are taken is common practice and acceptable to patients, their caregivers and health providers.

Feasibility

No research evidence

In the Australian context in which most prostate biopsies are undertaken under general anaesthesia there are no barriers to a single biopsy procedure in which both targeted biopsy cores and systematic biopsy cores are taken.

In contrast, eliminating a systematic biopsy and undertaking a targeted biopsy followed by a second biopsy if a clinical suspicion of prostate cancer remains on follow-up, would be more burdensome to a significant proportion of those patients with a negative targeted biopsy and the healthcare system.

Rationale

For this recommendation, several protocols were examined to determine the best biopsy procedure for patients with mpMRI PI-RADS 3 lesions for the detection of Clinically significant prostate cancer (ISUP ≥ 2).

Overall, the evidence suggested that for patients with PI-RADS 3 lesions, there are important harms of not diagnosing clinically significant disease if systematic biopsy is not undertaken in addition to MRI-targeted biopsy.

The important harms of not diagnosing clinically significant disease on biopsy in this population outweighs any possible benefits which are currently either uncertain or unknown.

No areas of major debate about the evidence and this recommendation were identified. This recommendation was reached with full consensus.

Clinical question/ PICO

Population: Males with mpMRI PI-RADS 3 lesions (biopsy naïve)
Intervention: MRI-targeted biopsy
Comparator: MRI-targeted biopsy plus ≥ 20-core systematic biopsy

Summary

Three studies were identified that investigated the use of MRI-targeted biopsy alone for men with PI-RADS 3 lesions with elevated PSA levels undergoing initial prostate biopsy *[48]*, *[50]*, *[53]*. A meta-analysis of the results from these studies showed that a clinically important number of clinically significant (ISUP grade ≥ 2) prostate cancers (>50/1000) will not be detected if a ≥ 20 core systematic biopsy is not undertaken in addition to a targeted biopsy if the prevalence of clinically significant prostate cancer is 30%. The certainty of evidence was high. No evidence was found for the detection of ISUP grade 1 or ISUP grade ≥ 3 prostate cancer.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** Targeted biopsy plus ≥ systematic biopsy	**Intervention** Targeted biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinically significant (ISUP Grade ≥ 2) prostate cancer not detected where the prevalence of clinically significant disease is 30%	Based on data from 211 participants in 3 studies.	For men with a mpMRI score 3 lesion if undertake only targeted biopsies the number of undetected ISUP Grade ≥ 2 prostate cancers in a population of 1000 is 111 (95% CI: 60, 165) based on a summary relative sensitivity of 0.63 (95% CI: 0.45, 0.80)		**High**	For biopsy-naïve men with a mpMRI score 3 lesion a clinically important number of clinically significant cancers will not be detected if a ≥ 20 core systematic biopsy is not undertaken in addition to a targeted biopsy.

Outcome Timeframe	**Study results and measurements**	**Comparator** Targeted biopsy plus ≥ systematic biopsy	**Intervention** Targeted biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
8 Critical		No relevant studies identified.			
ISUP Grade ≥ 3 prostate cancer detection					
ISUP Grade 1 prostate cancer detection		No relevant studies identified.			

References

48. Hansen NL, Barrett T, Kesch C, Pepdjonovic L, Bonekamp D, O'Sullivan R, et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer. BJU international 2018;122(1):40-49 Pubmed Journal

50. Mortezavi A, Märzendorfer O, Donati OF, Rizzi G, Rupp NJ, Wettstein MS, 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. The Journal of urology 2018;200(2):309-318 Pubmed Journal

53. Bonekamp D, Schelb P, Wiesenfarth M, Kuder TA, Deister F, Stenzinger A, et al. Histopathological to multiparametric MRI spatial mapping of extended systematic sextant and MR/TRUS-fusion-targeted biopsy of the prostate. European radiology 2019;29(4):1820-1830 Pubmed Journal

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Clinical question/ PICO

Population: Males with mpMRI PI-RADS 3 lesions (biopsy naïve)
Intervention: MRI-targeted biopsy plus 12-core systematic biopsy
Comparator: MRI-targeted biopsy plus ≥20-core systematic biopsy

Summary

Systematic searches of the literature did not identify any relevant studies reporting on the detection of clinically significant and insignificant prostate cancers if the number of systematic biopsy cores are reduced from ≥20 to 12-20 when performing systematic biopsy plus MRI-targeted biopsies for men with mpMRI PI-RADS 3 lesions.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** MRI-targeted biopsy plus ≥20-core systematic biopsy	**Intervention** MRI-targeted biopsy plus 12-core systematic biopsy	**Certainty of the evidence** (Quality of evidence)
Clinically significant (ISUP Grade ≥ 2) prostate cancer detection		No relevant studies identified.		
ISUP Grade ≥ 3 prostate cancer detection		No relevant studies identified.		
ISUP Grade 1 prostate cancer detection		No relevant studies identified.		

Clinical question/ PICO

Population: Males undergoing prostate biopsy
Intervention: MRI-targeted biopsy alone
Comparator: MRI-targeted biopsy plus 12-core systematic biopsy

Summary

Based on evidence from one randomised controlled trial that used a transrectal biopsy approach, the difference in the number of hospitalisations within 30 days of biopsy was clinically unimportant (<50/1000) if MRI-targeted biopsies only rather than MRI-targeted biopsies plus a systematic biopsy was undertaken *[211]*. The certainty of evidence was low due to very serious concerns regarding indirectness. No evidence was found for the outcome of longer-term erectile dysfunction ≥ 1-year post-biopsy.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** MRI-targeted biopsy alone	**Certainty of the evidence** (Quality of evidence)	**Summary**
Hospitalisation post-biopsy 30 days 9 Critical	Relative risk 0.29 (CI 95% 0.03 — 2.57) Based on data from 649 participants in 1 studies.	**12** per 1000 Difference:	**3** per 1000 **8.5 fewer per 1000** (CI 95% 11 fewer — 18 more)	**Low** Downgraded by two levels due to very serious concerns re: indirectness	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

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** MRI-targeted biopsy alone	**Certainty of the evidence** (Quality of evidence)	**Summary**
		No relevant studies identified.			unimportant difference in the number of hospitalisations within 30 days of biopsy.
Erectile dysfunction post-biopsy ≥ 1 year					

References

211. Hugosson J, Månsson M, Wallström J, Axcrona U, Carlsson SV, Egevad L, et al. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. New England Journal of Medicine 2022;387(23):2126-2137

Clinical question/ PICO

Population: Males undergoing prostate biopsy
Intervention: MRI-targeted biopsy plus 12-core systematic biopsy
Comparator: ≥20-core systematic biopsy

Summary

Based on evidence from one randomised controlled trial that used a transrectal biopsy approach, the difference in the number of hospitalisations post-biopsy was clinically unimportant (<50/1000) if MRI-targeted biopsies plus a 12-core systematic biopsy, rather than a 20-core systematic biopsy alone was undertaken *[155]*. The certainty of evidence was very low due to serious concerns regarding imprecision and indirectness. No evidence was found for the outcome of longer-term erectile dysfunction ≥ 1-year post-biopsy.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** MRI-targeted biopsy plus 12-core systematic biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Hospitalisation post-biopsy No timeframe 9 Critical	Relative risk 0.98 (CI 95% 0.06 — 15.28) Based on data from 105 participants in 1 studies.	**19** per 1000 Difference:	**19** per 1000 **0.2 fewer per 1000** (CI 95% 18 fewer — 274 more)	**Very low** Downgraded by three levels due to extremely serious concerns re: imprecision and serious concerns re: indirectness	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

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** MRI-targeted biopsy plus 12-core systematic biopsy	**Certainty of the evidence** (Quality of evidence)	**Summary**
		No relevant studies identified.			clinically unimportant difference in the number of hospitalisations due to biopsy complications.
Erectile dysfunction post-biopsy ≥ 1 year					

References

155. Dadpour M, Soltani AM, Ghafoori M, Basiri A, Borumandnia N, Nayebzade A, et al. Ultrasound/MRI-targeted biopsy versus saturated trans-rectal ultrasound guided biopsy of prostate in patients with primary negative conventional biopsy and still elevated PSA: a prospective randomized clinical trial. American Journal of Clinical and Experimental Urology 2023;11(4):312

Good practice statement

7.3 If the mpMRI is not suspicious of prostate cancer (PI-RADS 1 or 2), we propose systematic biopsies may still be performed if there is clinical concern, such as a digital rectal examination suspicious of prostate cancer, or a high risk of clinically significant prostate cancer.

Review by 2030, subject to emerging evidence

Good practice statement

7.4 When performing prostate biopsy for the early detection of prostate cancer, an ultrasound-guided transperineal approach is preferred as there is less risk of post-biopsy infection. In addition, the ultrasound images are in the axial plane as are the MRI images which facilitates more accurate target biopsies.

Review by 2030, subject to emerging evidence

Good practice statement

7.5 In most circumstances, prior to considering prostate biopsy for the early detection of prostate cancer, patients should have had a urological consultation which may include a history, discussion of benefits and possible harms of diagnosis, clinical examination, PSA testing and mpMRI.

Review by 2030, subject to emerging evidence

Good practice statement

7.6 The optimal number of cores for targeted biopsy should be at least 3-4.

As the number of systematic biopsy cores increases, the rate of diagnosis of clinically significant and insignificant prostate cancers rises. In addition, increased number of systematic cores may also increase the risk of complications arising such as bleeding, urinary retention, erectile dysfunction, and/or urinary infection.

Review by 2030, subject to emerging evidence

Good practice statement

7.7 In patients whose biopsies are benign, subsequent management will vary according to their risk profile. A discussion of their individual preferences is advised.

Options for ongoing management may include resumption of their previous PSA testing protocol, repeat imaging or repeat biopsy at varying intervals depending on their risk profile.

Review by 2030, subject to emerging evidence

Section E: Management

8. Active surveillance

Active surveillance is a monitoring strategy for men with clinically localised prostate cancer. It aims to minimize treatment-related toxicity without compromising survival by achieving correct timing for curative treatment (definitive treatment) for those who may eventually require it.

In the 2016 Guidelines, active surveillance was recommended as a treatment option for men with low- and intermediate risk prostate cancers. However, the data at the time was inconsistent regarding the best active surveillance protocols to use *[1]*.

Since 2016 the uptake of active surveillance as a first line treatment for low- or intermediate- risk prostate cancer has increased. Data from the Prostate Cancer Outcomes Registry Australia and New Zealand (PCOR-ANZ) show that that 80% (1,646/2,070) of men with low-risk prostate cancer chose active surveillance in 2021 which up from 66% (789/1,202) in 2015 *[55]*.

8.1 Criteria for choosing active surveillance

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? (Clinical question 10)

For the 2016 guidelines a systematic review was undertaken of randomised and non-randomised controlled studies to determine how the long term outcomes for men who chose active surveillance compared with long-term outcomes for those who opted for immediate definitive treatment. Relevant high quality RCT evidence could not be found. Recommendations were developed based on data from three cohort studies found *[56],[57],[58]* and evidence from a systematic review undertaken by the National Institute for Health and Care Excellence's (NICE) Clinical Guideline for Prostate Cancer: Diagnosis and Treatment (UK National Collaborating Centre for Cancer 2014) *[1]*.

Following the publication of the 2016 guidelines the results of the ProtecT trial*[44],[46]*, an RCT comparing active surveillance with immediate treatment, were published. To address our clinical question and update the 2016 recommendations, we focused exclusively on RCTs that compared active surveillance with immediate definitive treatment.

Good practice statement

8.1.1 The definition of active surveillance is a monitoring strategy for patients with clinically localised prostate cancer.

The intention of active surveillance is to minimise treatment-related toxicity without compromising survival by achieving correct timing for curative treatment for those who may eventually require it.

Review by 2030, subject to emerging evidence

Consensus recommendation

8.1.2 We propose that active surveillance be offered to patients with low-risk prostate cancer and may be offered to some patients with intermediate risk prostate cancer as below.

In patients diagnosed with prostate cancer, if all the following criteria are met*:

- PSA<10 µg/L
- Clinical stage T1-T2a
- Multiparametric magnetic resonance imaging (mpMRI) Prostate Imaging Reporting and Data System (PI-RADS) 3 or less
- PSA density (PSAD) 0.15 µg/L/mL or less.

Then,

1. Offer active surveillance to patients with International Society of Urological Pathology (ISUP) Grade Group 1
2. Consider offering active surveillance to patients with ISUP Grade Group 2 with less than or equal to 10% of Gleason pattern 4.

*Note that in selected cases, subject to a patient's individual circumstances, active surveillance may still be offered if PSA is >10 µg/L, or clinical stage is T2b or T2c, or mpMRI PI-RADS >3, or PSAD >0.15 µg/L/mL.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Benefits/desirable effects

For men diagnosed with localised prostate cancer undergoing active surveillance based only on PSA testing, results for the benefits at 15 years follow-up are as follows:

- For men **aged <65 years,** there were **no results** for quality of life outcomes. There was a **small** (clinically important) decrease in prostate cancer mortality compared with immediate radiotherapy but not prostatectomy.
- For men **aged ≥ 65 years,** there were **no results** for quality of life outcomes.
- For men with **low D'Amico risk score,** there were **no results** for quality of life outcomes.
- For men with **intermediate D'Amico risk score,** there were **no results** for quality of life outcomes and a **small** (clinically important) decrease in prostate cancer mortality when compared with immediate radiotherapy but not prostatectomy.
- For men with **high D'Amico risk score,** there were **no results** for quality of life outcomes and a **large** (clinically important) decrease in prostate cancer mortality compared with immediate prostatectomy (there was no data available for comparison with immediate radiotherapy)

Harms/ undesirable effects

For men diagnosed with localised prostate cancer undergoing active surveillance based only on PSA testing, results for the harms at 15 years follow-up are as follows:

- For men **aged <65 years,** there were **no results** for overall mortality, metastases or anxiety and **no clinically important increase in** prostate cancer mortality with immediate radiotherapy or prostatectomy.
- For men **aged ≥ 65 years,** there were **no results** for overall mortality, metastases or anxiety, but there was a **moderate (clinically important) increase** in prostate cancer mortality compared with immediate radiotherapy or prostatectomy
- For men with **low D'Amico risk score,** there were **no results** for overall mortality, metastases or anxiety, but there was a clinically **unimportant or borderline increase** in prostate cancer mortality compared with immediate prostatectomy **but not** radiotherapy
- For men with **intermediate D'Amico risk score,** there were **no results** for overall mortality, metastases or anxiety and **no clinically important increase** in prostate cancer mortality compared with immediate radiotherapy or prostatectomy.
- For men with **high D'Amico risk score,** there were **no results** for mortality, metastases or anxiety and **no clinically important increase** in prostate cancer mortality compared with immediate radiotherapy or prostatectomy.

Balance of benefits and harms/ desirable and undesirable effects

For men diagnosed with localised disease undergoing active surveillance based only on PSA testing, the balance of benefits and harms are as follows:

- for men **aged < 65 years,** the benefits were counterintuitive and there were no reported clinically important harms when compared with immediate definitive therapy - No difference between alternatives.
- for men **aged ≥ 65 years,** there was no evidence for benefits and a **moderate (clinically important) increase** in harms when compared with immediate definitive therapy - Important harms.
- for men **with low D'Amico risk score** when compared with immediate definitive therapy there was no evidence for benefits and a **borderline clinically unimportant increase** in harms when compared with immediate prostatectomy - No difference in alternatives
- for men **with intermediate D'Amico risk score** when compared with immediate definitive therapy the benefits were counterintuitive and there were no reported clinically important harms when compared with immediate definitive therapy - No difference between alternatives
- for men **with high D'Amico risk score** when compared with immediate definitive therapy the benefits were counterintuitive and there were no reported clinically important harms when compared with immediate definitive therapy - No difference between alternatives

Certainty of the evidence

Very low

The certainty of the evidence was rated low or very low for each of the outcomes for each of the populations for which there was data.

The low or very low ratings were based on

- serious concerns about indirectness as all harms and almost all benefits were derived from a RCT in which 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy and particularly in the case of D'Amico risk score subgroups, Gleason scores for a substantial proportion of participants would have been determined prior to the 2005 ISUP reclassification and will differ from current practice for some
- serious, very serious or extremely serious concerns about imprecision; and/or
- serious concerns about the risk of bias due to subgroup analyses resulting in an increased risk that those in intervention will differ from those in control group as the subgroup (D'Amico risk score subgroups) was not a minimisation variable in the randomisation

The serious concerns regarding indirectness and risk of bias may explain the counter intuitive findings for some risk groups.

Values and preferences

Substantial variability is expected or uncertain

Australian data, show that sexual function at 12 months is still a significant concern for Australian men with localised disease *[55]*.

Expert opinion suggests that here will be variability in how individuals with localised prostate cancer value the outcomes of sexual, urinary and bowel quality of life at 2 years and the risk of metastases, overall mortality and prostate cancer mortality at 15 years. Recommendations will be highly dependent on an individual's risk of disease progression, risk factors and personal circumstances necessitating an individualised approach with shared decision making.

Resources and other considerations

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability - *Important issues, or potential issues not investigated*

The acceptability of active surveillance protocols depends on the acceptability and frequency of the different modalities used to monitor for disease progression and will likely vary with individual risk of progression.

Biopsy is a disincentive to active surveillance. Avoidance of biopsy is linked to lack of adherence to protocols.

MRI is more acceptable than biopsy. In the Goteborg-2 trial screening participants reported MRI to be less bothersome than biopsy *[54]*.

Risk-stratified protocols are more tolerable.

Shared decision making and clear communications about the protocol are essential for the optimization of acceptability.

Feasibility - *No important issues with recommended alternative*

There are no important barriers to active surveillance in Australia. Active surveillance is an accepted and established management option for men with localised disease in Australia.

Urologists in Australia have become more comfortable with active surveillance. They are more confident in communicating the benefits of active surveillance and what it involves and in recommending active surveillance to their patients as a management option for localised disease. This increase in confidence will likely alleviate the psychological burden associated with active surveillance felt by some men.

Rationale

Two RCTs were found that compared active surveillance with immediate definitive treatment for the management of localised prostate cancer. These were the ProtecT trial trial *[44]*, *[46]*,and the PREFERE trial *[45]*. Both trials recruited men with localised disease and the ProtecT trial provided results for different patient subgroups.

Neither trial provided compelling evidence to support offering active surveillance to men with localised disease or specific subgroups of men with localised disease. Firstly, neither trial provided quality evidence of clinically important benefits so there was no clear evidence that the benefits of the active surveillance protocols used in either trial outweighed any possible harms. Secondly, the certainty of the evidence was low to very low as there were serious concerns regarding imprecision of effect estimates, risk of bias and/or indirectness of the results to the clinical question. Of particular concern is that in the ProtecT trial which provided almost all the evidence, it is likely that a substantial proportion of participants did not have localised disease at recruitment. Thirdly, neither trial used active surveillance protocols similar to those used currently employed in Australian practice which include multiparametric MRI imaging and targeted biopsies to monitor for disease progression.

In the absence of any clear evidence supporting offering active surveillance for the management of men with localised disease or subgroups thereof, the working group was unable to make any evidence-based recommendations as to which men should be offered active surveillance. Active surveillance is widely used in Australia to manage men with low- and, in some cases, intermediate - risk prostate cancer. To provide some guidance the working group developed this consensus-based recommendation and several good practice statements based on a consideration of recent international consensus-based guidelines, clinical expertise and experience.

No areas of major debate about the evidence and this recommendation were identified. This recommendation was reached with full consensus.

Clinical question/ PICO

Population: Individuals with biopsy- confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance
Comparator: Immediate radical prostatectomy

Summary

Two RCTs were found that compared active surveillance with immediate definitive treatment for the management of localised prostate cancer. These were the ProtecT trial trial *[44]*, *[46]* and the PREFERE trial *[45]*. The ProtecT trial provided all of the long-term clinical results and almost all of the patient reported outcome results. The PREFERE trial reported cancer-related quality of life results. Neither trial used active surveillance protocols incorporating multiparametric MRI.

There was no clear evidence that the active surveillance based only PSA testing used in the ProtecT trial achieved mortality results equivalent to those achieved by immediate prostatectomy for men with localised disease. It is uncertain as to whether there was any clinically important difference in prostate cancer mortality between active surveillance and immediate prostatectomy and whether there is a small increase in all cause deaths with active surveillance. Furthermore, there is a possibility that active surveillance as practised in this trial may increase the risk of metastatic disease.

For the quality-of-life related outcomes, either little difference is seen between active surveillance and immediate prostatectomy and/or it is uncertain as to whether there are small benefits with active surveillance.

For all outcomes the certainty of evidence was low to very low due to serious concerns regarding the imprecision, risk of bias and/or indirectness of the evidence to the clinical question. Most of the results were derived from the ProtecT trial in which it is likely that a substantial proportion of participants had non-localised disease at recruitment considering that 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Additionally, recruitment for the trial was carried out between 1999-2009 so it is likely that the Gleason scores for some of those recruited prior to 2005 would be different if determined today using the 2005 ISUP classification system.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths 15 years	Hazard ratio 1.52 (CI 95% 0.72 — 3.22) Based on data from 1,098	22 per 1000	33 per 1000	**Very low** Downgraded by three levels due to	We are uncertain as to whether active surveillance results in a clinically unimportant^

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
9 Critical	participants in 1 studies.	Difference:	**11 more per 1000** (CI 95% 6 fewer — 47 more)	very serious concerns re imprecision and serious concerns re indirectness [1]	increase in prostate cancer mortality when compared with immediate prostatectomy.
All-cause deaths 15 years 8 Critical	Hazard ratio 1.12 (CI 95% 0.87 — 1.45) Based on data from 1,098 participants in 1 studies.	**212** per 1000 Difference:	**234** per 1000 **22 more per 1000** (CI 95% 25 fewer — 80 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness	We are uncertain as to whether active surveillance results in a clinically important small^ increase in mortality when compared with immediate prostatectomy.
Metastatic disease 15 years 9 Critical	Hazard ratio 2.13 (CI 95% 1.32 — 3.45) Based on data from 1,098 participants in 1 studies.	**47** per 1000 Difference:	**97** per 1000 **50 more per 1000** (CI 95% 15 more — 106 more)	**Low** Downgraded by two levels due to serious concerns re imprecision and indirectness.	Active surveillance may result in a clinically important^^ increase in metastatic prostate cancer diagnoses when compared with immediate prostatectomy.
Sexual quality of life [2] 2 years 8 Critical	Measured by: EPIC sexual summary score Scale: 0 — 100 High better Based on data from 757 participants in 1 studies. (Randomized controlled)	**33.4** (Mean) Difference:	**49.2** (Mean) **MD 14.8 higher** (CI 95% 11.2 higher — 18.4 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision	We are uncertain as to whether active surveillance results in a clinically important (small)*^ increase in sexual quality of life when compared with immediate prostatectomy
Sexual bother [3] 2 years 8 Critical	Measured by: EPIC sexual bother score Scale: 0 — 100 High better Based on data from 766 participants in 1 studies. (Randomized controlled)	**47** (Mean) Difference:	**62.2** (Mean) **MD 15.2 higher** (CI 95% 10.3 higher — 20.1 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision	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] 2 years 8 Critical	Measured by: EPIC bowel summary score Scale: 0 — 100 High better Based on data from 800 participants in 1 studies. (Randomized controlled)	**93.8** (Mean) Difference:	**93.2** (Mean) **MD 0.6 lower** (CI 95% 1.8 lower — 0.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in bowel quality of life when compared with immediate prostatectomy.
Bowel bother [5] 2 years	Measured by: EPIC bowel bother score Scale: 0 — 100 High better Based on data from 800	**95.1** (Mean)	**94.2** (Mean)	**Low** Downgraded by two levels due to serious concerns re	Active surveillance may result in a clinically unimportant*^ difference in bowel bother when

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
8 Critical	participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.9 lower** (CI 95% 2.4 lower — 0.6 higher)	risk of bias and indirectness	compared with immediate prostatectomy.
Urinary quality of life [6] 2 years 8 Critical	Measured by: EPIC urinary summary score Scale: 0 — 100 High better Based on data from 794 participants in 1 studies. (Randomized controlled)	88.1 (Mean) Difference:	90.3 (Mean) **MD 2.2 higher** (CI 95% 0.6 higher — 3.8 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in urinary quality of life when compared with immediate prostatectomy.
Urinary bother [7] 2 years 8 Critical	Measured by: EPIC Urinary bother score Scale: 0 — 100 High better Based on data from 790 participants in 1 studies. (Randomized controlled)	89 (Mean) Difference:	88.6 (Mean) **MD 0.4 lower** (CI 95% 2.3 lower — 1.5 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in urinary bother when compared with immediate prostatectomy.
Cancer-related quality of life [8] 2 years 8 Critical	Measured by: QLQ-C30 score Scale: 0 — 100 High better Based on data from 177 participants in 1 studies. (Randomized controlled)	75.3 (Mean) Difference:	72.8 (Mean) **MD 2.5 lower** (CI 95% 12.7 lower — 7.7 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and imprecision	Active surveillance may result in a clinically unimportant*^ difference in cancer-related quality of life when compared with immediate prostatectomy.
Anxiety [9] 2 years 8 Critical	Measured by: HADS anxiety sub score Scale: 0 — 21 Lower better Based on data from 942 participants in 1 studies. (Randomized controlled)	3.6 (Mean) Difference:	3.9 (Mean) **MD 0.3 higher** (CI 95% 0.1 lower — 0.8 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active may result in a clinically unimportant*^ difference in anxiety when compared with immediate prostatectomy.
		^ 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			

1. **Indirectness: serious.** Differences between the population of interest and those studied - significant proportion of participants likely had non-localised disease.. **Publication bias: no serious.**

2, 3, 4, 5, 6, 7, 8, 9. Sexual quality of life as measured by EPIC sexual summary score. The range is 0-100 with higher being better.

References

44. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. The New England journal of medicine 2023;388(17):1547-1558 Pubmed Journal

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46. Donovan JL, Hamdy FC, Lane JA, Young GJ, Metcalfe C, Walsh EI, et al. Patient-Reported Outcomes 12 Years after Localized Prostate Cancer Treatment. NEJM evidence 2023;2(4):EVIDoa2300018 Pubmed Journal

Clinical question/ PICO

Population: Individuals with biopsy- confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance
Comparator: Immediate radical prostatectomy by subgroups

Summary

The ProtecT trial *[44]* provides subgroup analyses by age and D'Amico risk score for the outcome of 15-year prostate cancer mortality. The certainty of evidence was very low for all the subgroup results. As with the results for the entire trial population there were serious concerns regarding imprecision of the effect estimates and the indirectness of the data to the clinical question. In addition there were serious concerns regarding the risk of bias for the D'Amico risk groups as D'Amico risk score was not a minimisation variable in the randomisation process increasing the risk that those undergoing active surveillance differ from those who underwent immediate prostatectomy, and the counter-intuitive decrease in prostate cancer deaths with active surveillance for the subgroup of men with a high D'Amico risk score. As a result the evidence was so uncertain that it was not possible to draw any conclusions as to the impact of active surveillance on prostate cancer mortality in different age groups or D'Amico risk score subgroups.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy by subgroups	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths for individuals <65 years of age 15 years 9 Critical	Hazard ratio 0.87 (CI 95% 0.26 — 2.86) Based on data from 693 participants in 1 studies.	**17** per 1000 Difference:	**15** per 1000 **2 fewer per 1000** (CI 95% 13 fewer — 31 more)	**Very low** Downgraded by three levels due to serious concerns re indirectness and very serious concerns re imprecision [1]	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.
Prostate cancer-specific deaths for individuals ≥65 years of age 15 years	Hazard ratio 2.13 (CI 95% 0.81 — 5.88) Based on data from 247 participants in 1 studies. (Randomized controlled)	**30** per 1000 Difference:	**63** per 1000 **33 more per 1000**	**Very low** Downgraded by three levels due to serious concerns re indirectness and	For men aged ≥ 65 years we are uncertain as to whether active surveillance results in a clinically important

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy by subgroups	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
9 Critical			(CI 95% 6 fewer — 134 more)	very serious concerns re imprecision. [2]	(moderate)^ increase in prostate cancer mortality when compared with immediate prostatectomy.
Prostate cancer-specific deaths for individuals with a low D'Amico risk score 15 years 9 Critical	Hazard ratio 2.27 (CI 95% 0.7 — 7.69) Based on data from 671 participants in 1 studies.	**12** per 1000 Difference:	**26** per 1000 **14.3 more per 1000** (CI 95% 3 fewer — 75 more)	**Very low** Downgraded by three levels due to serious concerns re risk of bias and indirectness, and very serious concerns re imprecision. [3]	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 prostatectomy.
Prostate cancer-specific deaths for individuals with an intermediate D'Amico risk score 15 years 9 Critical	Hazard ratio 1.47 (CI 95% 0.25 — 9.09) Based on data from 247 participants in 1 studies. (Randomized controlled)	**17** per 1000 Difference:	**25** per 1000 **8.1 more per 1000** (CI 95% 13 fewer — 127 more)	**Very low** Downgraded by three levels due to serious concerns re risk of bias and indirectness, and extremely serious concerns re imprecision. [4]	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.
Prostate cancer-specific deaths for individuals with a high D'Amico risk score 15 years 9 Critical	Hazard ratio 0.38 (CI 95% 0.08 — 1.89) Based on data from 103 participants in 1 studies. (Randomized controlled)	**111** per 1000 Difference:	**44** per 1000 **67.1 fewer per 1000** (CI 95% 102 fewer — 88 more)	**Very low** Downgraded by three levels due to serious concerns re risk of bias and indirectness, and extremely serious concerns re imprecision. [5]	For men with an intermediate D'Amico risk score we are uncertain as to whether active surveillance results in a clinically important (large)^ increase in prostate cancer mortality when compared with immediate prostatectomy.
		^ Using thresholds of 15, 30 and 60 deaths /1000 for small (minimal clinically important difference), moderate and large effects			

1, 2, 3, 4, 5. **Indirectness: serious.** Differences between the population of interest and those studied - significant proportion of participants likely had non-localised disease.. **Publication bias: no serious.**

References

44. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for

Prostate Cancer. The New England journal of medicine 2023;388(17):1547-1558 Pubmed Journal

Clinical question/ PICO

Population: Individuals with biopsy- confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance
Comparator: Immediate external beam radiotherapy

Summary

Evidence for this PICO was derived from a single randomised controlled trial, the ProtecT trial *[44]*, *[46]*, that compared active surveillance with immediate external beam radiotherapy (EBRT) for the management of localised prostate cancer. When compared with immediate EBRT there is a possibility that active surveillance based only PSA level monitoring may increase the risk of metastatic disease however it is uncertain as to whether there is no clinically important difference for the outcome of prostate specific cancer mortality or whether there is a small increase in all cause deaths with active surveillance. For the quality-of-life related outcomes, either little difference was seen between active surveillance and EBRT and/or it is uncertain as to whether there is a small reduction in bowel bother with active surveillance.

The certainty of the evidence was low to very low with serious concerns regarding the imprecision of effect estimates, risk of bias and indirectness. For the Protect trial there were major concerns regarding indirectness as it is likely that a substantial proportion of participants in this trial had non-localised disease at recruitment considering that 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Additionally, recruitment for the trial was carried out between 1999-2009 so it is likely that the Gleason scores for some of those recruited prior to 2005 would be different if determined today using the 2005 ISUP classification system.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths 15 years 9 Critical	Hazard ratio 1.14 (CI 95% 0.57 — 2.27) Based on data from 1,090 participants in 1 studies.	**29** per 1000 Difference:	**33** per 1000 **4 more per 1000** (CI 95% 12 fewer — 36 more)	**Very low** Downgraded by three levels due to very serious concerns re imprecision and serious concerns re indirectness [1]	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 years 8 Critical	Hazard ratio 1.14 (CI 95% 0.88 — 1.47) Based on data from 1,090 participants in 1 studies.	**211** per 1000 Difference:	**237** per 1000 **26 more per 1000** (CI 95% 23 fewer — 83 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness.	We are uncertain as to whether active surveillance results in a clinically important (small)^ increase in mortality when compared with immediate radiotherapy.
Metastatic disease 15 years	Hazard ratio 2.08 (CI 95% 1.3 — 3.33) Based on data from 1,090	**50** per 1000	**100** per 1000	**Low** Downgraded by two levels due to	Active surveillance may result in a clinically important (small)^^ increase in metastatic

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
9 Critical	participants in 1 studies.	Difference:	**51 more per 1000** (CI 95% 15 more — 107 more)	serious concerns re imprecision and indirectness.	prostate cancer diagnoses when compared with immediate radiotherapy.
Sexual quality of life [2] 2 years 8 Critical	Measured by: EPIC sexual summary score Scale: 0 — 100 High better Based on data from 740 participants in 1 studies. (Randomized controlled)	43.4 (Mean) Difference:	48.2 (Mean) **MD 4.8 higher** (CI 95% 1 higher — 8.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness.	Active surveillance may result in a clinically unimportant*^ difference in sexual quality of life when compared with immediate radiotherapy.
Sexual bother [3] 2 years 8 Critical	Measured by: EPIC sexual bother score Scale: 0 — 100 High better Based on data from 744 participants in 1 studies. (Randomized controlled)	57.9 (Mean) Difference:	61.2 (Mean) **MD 4.3 higher** (CI 95% 0.7 lower — 9.3 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness.	Active surveillance may result in a clinically unimportant*^ difference in sexual bother when compared with immediate radiotherapy
Bowel quality of life [4] 2 years 8 Critical	Measured by: EPIC bowel summary score Scale: 0 — 100 High better Based on data from 785 participants in 1 studies. (Randomized controlled)	89.3 (Mean) Difference:	93.2 (Mean) **MD 3.9 higher** (CI 95% 2.3 higher — 5.5 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision	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 [5] 2 years 8 Critical	Measured by: EPIC bowel bother score Scale: 0 — 100 High better Based on data from 789 participants in 1 studies. (Randomized controlled)	89.2 (Mean) Difference:	94.2 (Mean) **MD 5 higher** (CI 95% 3 higher — 7 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision	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 [6] 2 years 8 Critical	Measured by: EPIC urinary summary score Scale: 0 — 100 High better Based on data from 785 participants in 1 studies. (Randomized controlled)	91.4 (Mean) Difference:	90.3 (Mean) **MD 1.1 lower** (CI 95% 2.6 lower — 0.4 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in urinary quality of life when compared with immediate radiotherapy.
Urinary bother [7] 2 years 8 Critical	Measured by: EPIC Urinary bother score Scale: 0 — 100 High better Based on data from 782 participants in 1 studies. (Randomized controlled)	90.3 (Mean) Difference:	88.6 (Mean) **MD 1.7 lower** (CI 95% 3.5 lower — 0.1 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in urinary bother when compared with immediate radiotherapy.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
Anxiety [8] 2 years 8 Critical	Measured by: HADS anxiety sub score Scale: 0 — 21 Lower better Based on data from 937 participants in 1 studies. (Randomized controlled)	**3.7** (Mean) Difference:	**3.9** (Mean) **MD 0.2 higher** (CI 95% 0.2 lower — 0.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in anxiety when compared with immediate radiotherapy.
		^ 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			

1. **Indirectness: serious.** Differences between the population of interest and those studied - significant proportion of participants likely had non-localised disease.. **Publication bias: no serious.**
2, 3, 4, 5, 6, 7, 8. Sexual quality of life as measured by EPIC sexual summary score. The range is 0-100 with higher being better.

References

44. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. The New England journal of medicine 2023;388(17):1547-1558 Pubmed Journal

46. Donovan JL, Hamdy FC, Lane JA, Young GJ, Metcalfe C, Walsh EI, et al. Patient-Reported Outcomes 12 Years after Localized Prostate Cancer Treatment. NEJM evidence 2023;2(4):EVIDoa2300018 Pubmed Journal

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Clinical question/ PICO

Population: Individuals with biopsy- confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance
Comparator: Immediate external beam radiotherapy by subgroups

Summary

The ProtecT trial *[44]* provides subgroup analyses by age and low and intermediate D'Amico risk scores for the outcome of 15-year prostate cancer mortality. For all subgroups the certainty of evidence was very low. As with the results for the entire trial population there were serious concerns regarding imprecision of the effect estimates and the indirectness of the data to the clinical question. In addition there were serious concerns regarding the risk of bias for the D'Amico risk groups as D'Amico risk score was not a minimisation variable in the randomisation process increasing the risk that those undergoing active surveillance differ from those who underwent immediate external beam radiotherapy

(EBRT), and the counter-intuitive decreases in prostate cancer deaths with active surveillance for the subgroups of men aged < 65 years or with an intermediate D'Amico risk score. As a result the evidence was so uncertain that it was not possible to draw any conclusions as to the impact of active surveillance on prostate cancer mortality in different age groups or in low and intermediate D'Amico risk score subgroups.

There was no data available comparing active surveillance and EBRT for the subgroup high D'Amico risk score.

More information can be found in the Technical Report.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy by subgroups	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths for individuals <65 years of age 15 years 9 Critical	Hazard ratio 0.49 (CI 95% 0.17 — 1.43) Based on data from 681 participants in 1 studies.	**29** per 1000 Difference:	**14** per 1000 **15 fewer per 1000** (CI 95% 24 fewer — 12 more)	**Very low** Downgraded by three levels due to serious concerns re indirectness and very serious concerns re imprecision. [1]	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.
Prostate cancer-specific deaths for individuals ≥65 years of age 15 years 9 Critical	Hazard ratio 2.33 (CI 95% 0.87 — 6.25) Based on data from 409 participants in 1 studies.	**29** per 1000 Difference:	**67** per 1000 **37.6 more per 1000** (CI 95% 4 fewer — 141 more)	**Very low** Downgraded by three levels due to serious concerns re indirectness and very serious concerns re imprecision. [2]	For men aged ≥ 65 years we are uncertain as to whether active surveillance results in a clinically important important (moderate)^ increase in prostate cancer mortality when compared with immediate radiotherapy.
Prostate cancer-specific deaths for individuals with a low D'Amico risk score 15 years 9 Critical	Hazard ratio 1.59 (CI 95% 0.56 — 4.35) Based on data from 671 participants in 1 studies.	**18** per 1000 Difference:	**28** per 1000 **10.5 more per 1000** (CI 95% 8 fewer — 56 more)	**Very low** Downgraded by three levels due to serious concerns re risk of bias and indirectness, and very serious concerns re imprecision. [3]	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.
Prostate cancer-specific deaths for individuals with an intermediate D'Amico risk score 15 years 9 Critical	Hazard ratio 0.61 (CI 95% 0.15 — 2.56) Based on data from 251 participants in 1 studies.	**41** per 1000 Difference:	**25** per 1000 **16 fewer per 1000** (CI 95% 35 fewer — 61 more)	**Very low** Downgraded by three levels due to serious concerns re risk of bias and indirectness, and extremely serious concerns re imprecision. [4]	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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy by subgroups	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths for individuals with a high D'Amico risk score 15 years 9 Critical	Hazard ratio 0 (CI 95% 0 — 0) Based on data from 93 participants in 1 studies.	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	5	No evidence available for men with a high D'Amico risk score.
		^ Using thresholds of 15, 30 and 60 deaths /1000 for small (minimal clinically important difference), moderate and large effects			

1, 2, 3, 4, 5. **Indirectness: serious.** Differences between the population of interest and those studied - significant proportion of participants likely had non-localised disease.. **Publication bias: no serious.**

References

43. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. The New England journal of medicine 2016;375(15):1415-1424 Pubmed Journal

44. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. The New England journal of medicine 2023;388(17):1547-1558 Pubmed Journal

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Good practice statement

8.1.3 When considering active surveillance, take into account other factors that may be associated with the risk of future pathological progression such as total cancer length or percentage core involvement at biopsy and tumour volume.

Active surveillance is not advised in patients with:

- Variant histology, including sarcomatoid, small cell, cribriform
- Histologic features, including intraduct, extra-prostatic extension, lymphovascular invasion and perineural invasion.

Review by 2030, subject to emerging evidence

Good practice statement

8.1.4 Perform mpMRI if no MRI has been performed before the initial biopsy.

Review by 2030, subject to emerging evidence

8.2 Monitoring protocols for active surveillance

What is the best monitoring protocol for active surveillance and what should be the criteria for intervention? (Clinical question 11)

For the 2016 Guidelines a systematic review was undertaken of randomised and non-randomised controlled studies comparing active surveillance with immediate treatment to identify active surveillance protocols with long term outcomes comparable to immediate treatment. Three cohort studies were included *[56]*, *[57]*, *[58]*. No randomised controlled trials (RCTs) were found that matched the search criteria. Following the publication of the 2016 Guidelines the results of the ProtecT trial *[44]*, *[46]*, an RCT comparing active surveillance with immediate treatment, were published. The 2016 guidelines did not consider comparisons of different active surveillance protocols. Consequently, to address this clinical question and update the guidelines two PICOs were developed and two systematic reviews undertaken to:

- Focus exclusively on RCTs that compared active surveillance with immediate definitive treatment
- Identify RCTs comparing different active surveillance protocols.

Consensus recommendation

8.2.1 We propose for patients with prostate cancer who are being managed by active surveillance offer:

- Initial three to six-monthly PSA measurements
- Digital rectal examination periodically
- Repeat multiparametric magnetic resonance imaging (mpMRI) may be offered after 12 to 24 months and again at three years, or earlier, if clinically indicated
- Repeat the prostate biopsy in the first 12 months at clinician's discretion e.g., where there is uncertainty regarding initial diagnostic biopsy, changes in PSA, digital rectal examination or mpMRI.

Subsequent repeat prostate biopsies are usually not required in less than three years unless there are changes in PSA, digital rectal examination or mpMRI.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Benefits/desirable effects

Using size of effects based on thresholds of 1, 2 and 4 times the minimal clinically important difference (MCID) for small (MCID), moderate and large effects.

For men diagnosed with localised prostate cancer **active surveillance based only on PSA testing** *when compared with immediate prostatectomy there was*

- **Small** (clinically important) increase in sexual quality of life at 2 years follow-up
- **Small** (clinically important) decrease in sexual bother at 2 years follow-up

when compared with immediate radiotherapy there was

- **Small** (clinically important) increase in bowel quality of life at 2 years follow-up

No clinically important benefits for other patient reported outcomes including urinary quality of life and urinary bother at 2 years

Harms/ undesirable effects

Using size of effects based on thresholds of 1, 2 and 4 times the minimal clinically important difference (MCID) for small (MCID), moderate and large effects.

For men diagnosed with localised prostate cancer **active surveillance based only on PSA testing** *when compared with immediate prostatectomy or radiotherapy there was*

- **Small** (clinically important) increase in metastatic disease at 15 years follow-up
- **Small** (clinically important) increase in all-cause mortality at 15 years follow-up

No clinically important increases in prostate cancer mortality at 15 years or anxiety at 2 years

Balance of benefits and harms/ desirable and undesirable effects

For men diagnosed with localised prostate cancer**r, active surveillance based only on PSA testing** *when compared with immediate definitive therapy* both the benefits and harms are **small** but clinically important.

Certainty of the evidence

Very low

The certainty of the evidence was rated low or very low for each of the outcomes.

The low or very ratings were based on

- serious concerns about indirectness as almost all outcomes were derived from a RCT in which 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy
- serious, very serious or extremely concerns about imprecision: and/or
- serious concerns about the risk of bias due to lack of blinding and baseline variables not being accounted for in analyses for most quality of life outcomes.

Values and preferences

Substantial variability is expected or uncertain

Australian data (PCOR) show that sexual function at 12 months is still a significant concern for Australian men with localised disease *[55]*.

Expert opinion suggests that there will be variability in how men with localised prostate cancer value the outcomes of sexual, urinary and bowel quality of life at 2 years and the risk of metastases, overall mortality and prostate cancer mortality at 15 years.

As recommendations will be highly dependent on individual risk of disease progression risk group, an individualised approach is recommended in which shared decision making will be essential.

Resources and other considerations

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability - Substantial variability is expected or uncertain

The acceptability of active surveillance protocols will depend on the acceptability and frequency of the different modalities used to monitor for disease progression and the risk of disease progression.

Biopsy is a disincentive to active surveillance. Avoidance of biopsy is linked to lack of adherence to protocols.

RCTs comparing **annual biopsy protocols** ((NCT 0183265 and NCT 02564549) and PREFERE trial *[45]* in which active surveillance involved **biopsy at 6 months, 12 months and then every 3 years** were terminated early suggest these protocols were unacceptable to many patients.

In contrast the ProtecT trial ran for over 10 years suggesting that the active surveillance protocol used in this trial, **surveillance based only on PSA testing**, is likely acceptable to most men however in the era of MRI surveillance PSA surveillance is not that useful.

MRI is more acceptable than biopsy. In the Goteborg-2 trial screening participants reported MRI to be less bothersome than biopsy *[54]*.

Risk-stratified protocols are more tolerable.

Shared decision making and clear communications about the protocol are essential for the optimization of acceptability.

Some will experience psychological issues, potential to discuss options for counselling (practice point).

Feasibility - Important issues, or potential issues not investigated

There are no important barriers to active surveillance in Australia. Active surveillance is an accepted and established management option for men with localised disease in Australia.

Urologists in Australia have become more comfortable with active surveillance. They are more confident communicating what is involved and its benefits and recommending active surveillance as a management option for localised disease. This increase in confidence will likely alleviate the psychological burden associated with active surveillance felt by some individuals.

Rationale

Two RCTs were found that compared active surveillance with immediate definitive treatment for the management of localised prostate cancer. These were the ProtecT trial trial *[44]*, *[46]*,and the PREFERE trial *[45]*. The ProtecT trial provided the long-term clinical results and almost all of the patient reported outcome results. Starting in 1999 this trial used an active surveillance protocol in which PSA testing alone was used to monitor for disease progression. The PREFERE trial used PSA testing and frequent biopsies to monitor those on active surveillance and reported cancer-related quality of life results.

Neither trial provided results that could be used to identify optimal active surveillance protocols for men with localised prostate cancer. There was no clear evidence that benefits of the active surveillance protocols used in either trial outweighed any possible harms with neither trial providing quality evidence of benefits in quality of life that were clinically important. The PREFERE trial was unable to provide evidence as to any long-term harms as it was terminated early due poor recruitment and the ProtecT trial raised the possibility that active surveillance as practiced in that trial may increase the risk of metastatic disease.

Based on the uncertainty of the evidence, the possible harms of monitoring using only PSA testing to monitor for disease progression and the lack of clear evidence of clinically important quality of life benefits the working group was unable to recommend either of these protocols. Both protocols have been superseded in Australian clinical practice with the introduction of multiparametric MRI imaging of the prostate and MRI-targeted biopsies. The incorporation of multiparametric MRI imaging and targeted biopsies has given clinicians and patients greater confidence in choosing active surveillance resulting in its increasing uptake since 2016. As prostate cancer is usually a slowly progressing disease we did not find any comparative evidence of clinical outcomes for contemporary active surveillance protocols incorporating MRI imaging and targeted biopsies. In the absence of any evidence relevant to current clinical practice the working group developed consensus-based recommendations based on clinical expertise and experience.

No areas of major debate about the evidence and this recommendation were identified. This recommendation was reached with full consensus.

Clinical question/ PICO

Population: Individuals with biopsy-confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance with different monitoring protocols
Comparator: Immediate radical prostatectomy

Summary

Two RCTs were found that compared active surveillance with immediate prostatectomy for the management of localised prostate cancer. These were the ProtecT trial *[43][46]* protocol in which PSA screening alone was used to monitor for disease progression, and the PREFERE trial in which biopsies in addition to PSA testing were used to monitor for disease progression *[45]*. The ProtecT trial provided the long-term clinical results and almost all of the patient reported outcome results and the PREFERE trial reported cancer-related quality of life results.

There was no clear evidence that the active surveillance protocol used in the ProtecT trial achieved mortality results equivalent to those achieved by immediate prostatectomy. It is uncertain as to whether there was any clinically important difference in prostate cancer mortality between active surveillance and prostatectomy and whether there is a small increase in all cause deaths with active surveillance. Furthermore, there is a possibility that active surveillance as practised in this trial may increase the risk of metastatic disease.

For the quality-of-life related outcomes, either little difference is seen between active surveillance and immediate prostatectomy and/or it is uncertain as to whether there are small benefits with active surveillance.

For all outcomes the certainty of evidence was low to very low due to serious concerns regarding the imprecision, risk of bias and/or indirectness of the evidence to the clinical question. Most of the results were derived from the ProtecT trial in which it is likely that a substantial proportion of participants had non-localised disease at recruitment considering that 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Additionally, recruitment for the trial was carried out between 1999-2009 so it is likely that the Gleason scores for some of those recruited prior to 2005 would be different if determined today using the 2005 ISUP classification system.

More information can be found in the Technical Report.

Note: the evidence in this PECO informed consensus recommendations 8.2.1 and 8.2.2.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance with different monitoring protocols	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths - Active surveillance with PSA monitoring alone 15 years 9 Critical	Hazard ratio 1.52 (CI 95% 0.72 — 3.22) Based on data from 1,098 participants in 1 studies.	22 per 1000 Difference:	33 per 1000 **11 more per 1000** (CI 95% 6 fewer — 47 more)	**Very low** Downgraded by three levels due to very serious concerns re imprecision and serious concerns re indirectness	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 - Active surveillance based on PSA monitoring alone 15 years 8 Critical	Hazard ratio 1.12 (CI 95% 0.87 — 1.45) Based on data from 1,098 participants in 1 studies.	212 per 1000 Difference:	234 per 1000 **22.4 more per 1000** (CI 95% 25 fewer — 80 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness	We are uncertain as to whether active surveillance results in a clinically important (small)^ increase in prostate cancer mortality when compared with immediate prostatectomy.
Metastatic disease - Active surveillance with PSA monitoring alone 15 years 9 Critical	Hazard ratio 2.13 (CI 95% 1.32 — 3.45) Based on data from 1,098 participants in 1 studies.	47 per 1000 Difference:	97 per 1000 **50 more per 1000** (CI 95% 15 more — 106 more)	**Low** Downgraded by two levels due to serious concerns re imprecision and indirectness	Active surveillance may result in a clinically important (small)^^ increase in metastatic prostate cancer diagnoses when compared with immediate prostatectomy.
Sexual quality of life - Active surveillance with PSA monitoring alone 2 years 8 Critical	Measured by: EPIC sexual summary score Scale: 0 — 100 High better Based on data from 757 participants in 1 studies.	33.4 (Mean) Difference:	49.2 (Mean) **MD 14.8 higher** (CI 95% 11.2 higher — 18.4 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision	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 - Active	Measured by: EPIC sexual bother score Scale: 0 — 100 High better	47 (Mean)	62.2 (Mean)	**Very low** Downgraded by three levels due to	We are uncertain as to whether active surveillance results in a

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance with different monitoring protocols	**Certainty of the evidence** (Quality of evidence)	**Summary**
surveillance with PSA monitoring alone 2 years 8 Critical	Based on data from 766 participants in 1 studies.	Difference:	**MD 15.2 higher** (CI 95% 10.3 higher — 20.1 higher)	serious concerns re risk of bias, indirectness and imprecision	clinically important (small)*^ decrease in sexual bother when compared with prostatectomy.
Bowel quality of life - Active surveillance with PSA monitoring alone 2 years 8 Critical	Measured by: EPIC bowel summary score Scale: 0 — 100 High better Based on data from 800 participants in 1 studies.	**93.8** (Mean) Difference:	**93.2** (Mean) **MD 0.6 lower** (CI 95% 1.8 lower — 0.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant difference in bowel quality of life when compared with immediate prostatectomy
Bowel bother - Active surveillance with PSA monitoring alone 2 years 8 Critical	Measured by: EPIC bowel bother score Scale: 0 — 100 High better Based on data from 800 participants in 1 studies.	**95.1** (Mean) Difference:	**94.2** (Mean) **MD 0.9 lower** (CI 95% 2.4 lower — 0.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in bowel bother when compared with immediate prostatectomy
Urinary quality of life - Active surveillance with PSA monitoring alone 2 years 8 Critical	Measured by: EPIC urinary summary score Scale: 0 — 100 High better Based on data from 794 participants in 1 studies.	**88.1** (Mean) Difference:	**90.3** (Mean) **MD 2.2 higher** (CI 95% 0.6 higher — 3.8 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in urinary quality of life when compared with immediate prostatectomy.
Urinary bother - Active surveillancewith PSA monitoring alone 2 years 8 Critical	Measured by: EPIC urinary bother score Scale: 0 — 100 High better Based on data from 790 participants in 1 studies.	**89** (Mean) Difference:	**88.6** (Mean) **MD 0.4 lower** (CI 95% 2.3 lower — 1.5 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant difference in urinary bother when compared with immediate prostatectomy
Anxiety - Active surveillance with PSA monitoring alone	Measured by: HADS anxiety sub score Scale: 0 — 21 Lower better	**3.6** (Mean)	**3.9** (Mean)	**Low** Downgraded by two levels due to serious concerns re	Active may result in a clinically unimportant*^ difference in anxiety when compared with immediate

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance with different monitoring protocols	**Certainty of the evidence** (Quality of evidence)	**Summary**
2 years 8 Critical	Based on data from 942 participants in 1 studies.	Difference:	**MD 0.3 higher** (CI 95% 0.1 lower — 0.8 higher)	risk of bias and indirectness	prostatectomy
Cancer-related quality of life - Active surveillance with PSA monitoring and biopsies at 6 and 12 months then every 3 years 2 years 8 Critical	Measured by: QLQ-C30 score Scale: 0 — 100 High better Based on data from 177 participants in 1 studies.	**75.3** (Mean) Difference:	**72.8** (Mean) **MD 2.5 lower** (CI 95% 12.7 lower — 7.7 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and imprecision	Active surveillance may result in a clinically unimportant*^ difference in cancer-related quality of life when compared with immediate prostatectomy
		^ 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			

Clinical question/ PICO

Population: Individuals with biopsy- confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance with PSA monitoring
Comparator: Immediate external beam radiotherapy

Summary

Evidence for this PICO was derived from a single randomised controlled trial, the ProtecT trial, in which active surveillance based only PSA level monitoring was compared with immediate prostatectomy or external beam radiotherapy *[44]*, *[46]*. When compared with immediate external beam radiotherapy (EBRT) there is a possibility that active surveillance based only PSA level monitoring may increase the risk of metastatic disease however it is uncertain as to whether there is no clinically important difference for the outcome of prostate specific cancer mortality or whether there is a small increase in all cause deaths with active surveillance. For the quality-of-life related outcomes, either little difference is seen between active surveillance and EBRT and/or it is uncertain as to whether there are small benefits with active surveillance.

For all outcomes the certainty of evidence was low to very low. There were serious concerns regarding the imprecision of effect estimates, risk of bias and indirectness. Major concerns regarding indirectness arose as it is likely that a substantial proportion of participants in this trial had non-localised disease at recruitment considering that 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Additionally, recruitment for the trial was carried out between 1999-2009 so it is likely that the Gleason scores for some of those recruited prior to 2005 would be different if determined today using the 2005 ISUP classification system.

More information can be found in the Technical Report.

Note: the evidence in this PECO informed consensus recommendations 8.2.1 and 8.2.2.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy	**Intervention** Active surveillance with PSA monitoring	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths 15 years 9 Critical	Hazard ratio 1.14 (CI 95% 0.57 — 2.27) Based on data from 1,090 participants in 1 studies.	**29** per 1000 Difference:	**33** per 1000 **4 more per 1000** (CI 95% 12 fewer — 36 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness	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 years 8 Critical	Hazard ratio 1.14 (CI 95% 0.88 — 1.47) Based on data from 1,090 participants in 1 studies.	**211** per 1000 Difference:	**237** per 1000 **26 more per 1000** (CI 95% 23 fewer — 83 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness	We are uncertain as to whether active surveillance results in a clinically important (small)^ increase in mortality when compared with immediate radiotherapy.
Metastatic disease 15 years 9 Critical	Hazard ratio 2.08 (CI 95% 1.3 — 3.33) Based on data from 1,090 participants in 1 studies.	**50** per 1000 Difference:	**101** per 1000 **51 more per 1000** (CI 95% 15 more — 107 more)	**Low** Downgraded by two levels due to serious concerns re imprecision and indirectness	Active surveillance may result in a clinically important (small)^^ increase in metastatic prostate cancer diagnoses when compared with immediate radiotherapy.
Sexual quality of life 2 years 8 Critical	Measured by: EPIC sexual summary score Scale: 0 — 100 High better Based on data from 740 participants in 1 studies.	**43.4** (Mean) Difference:	**48.2** (Mean) **MD 4.8 higher** (CI 95% 1 higher — 8.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in sexual quality of life when compared with immediate radiotherapy
Sexual bother 2 years 8 Critical	Measured by: EPIC sexual bother score Scale: 0 — 100 High better Based on data from 744 participants in 1 studies.	**57.9** (Mean) Difference:	**61.2** (Mean) **MD 4.3 higher** (CI 95% 0.7 lower — 9.3 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in sexual bother when compared with immediate radiotherapy

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy	**Intervention** Active surveillance with PSA monitoring	**Certainty of the evidence** (Quality of evidence)	**Summary**
Bowel quality of life 2 years 8 Critical	Measured by: EPIC bowel summary score Scale: 0 — 100 High better Based on data from 785 participants in 1 studies.	**89.3** (Mean) Difference:	**93.2** (Mean) **MD 3.9 higher** (CI 95% 2.3 higher — 5.5 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision.	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 2 years 8 Critical	Measured by: EPIC bowel bother score Scale: 0 — 100 High better Based on data from 789 participants in 1 studies.	**89.2** (Mean) Difference:	**94.2** (Mean) **MD 5 higher** (CI 95% 3 higher — 7 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision	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 2 years 8 Critical	Measured by: EPIC urinary summary score Scale: 0 — 100 High better Based on data from 785 participants in 1 studies.	**91.4** (Mean) Difference:	**90.3** (Mean) **MD 1.1 lower** (CI 95% 2.6 lower — 0.4 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in urinary quality of life when compared with immediate radiotherapy
Urinary bother 2 years 8 Critical	Measured by: EPIC urinary bother score Scale: 0 — 100 High better Based on data from 781 participants in 1 studies.	**90.3** (Mean) Difference:	**88.6** (Mean) **MD 1.7 lower** (CI 95% 3.5 lower — 0.1 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in urinary bother when compared with immediate radiotherapy.
Anxiety 2 years 8 Critical	Measured by: HADS anxiety sub score Scale: 0 — 21 Lower better Based on data from 937 participants in 1 studies.	**3.7** (Mean) Difference:	**3.9** (Mean) **MD 0.2 higher** (CI 95% 0.2 lower — 0.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in anxiety when compared with immediate radiotherapy.
		^ 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			

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy	**Intervention** Active surveillance with PSA monitoring	**Certainty of the evidence** (Quality of evidence)	**Summary**
		clinically important difference), moderate and large effects			

Clinical question/ PICO

Population: Individuals with biopsy-confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance
Comparator: Another active surveillance protocol

Summary

No randomised controlled trials were found that compared different active surveillance protocols.

More information can be found in the Technical Report.

Note: this PECO informed consensus recommendations 8.2.1 and 8.2.2.

Outcome Timeframe	**Study results and measurements**	**Comparator** Another active surveillance protocol	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)
All outcomes including: All-cause mortality, Prostate cancer-specific mortality, Metastasis, Health-related quality of life and Adverse patient-reported outcomes		No eligible RCTs were identified. Five potentially relevant ongoing trials were identified by searches of clinical trial registries or literature searches, two of which were terminated early or withdrawn. More information can be found in the technical report here **[URL NEEDED]**		

Consensus recommendation

8.2.2 We propose that for patients being managed by active surveillance, offer definitive treatment if:

- Pathological progression is detected on biopsy
- Patient preference.

Note: Progression on mpMRI is not an indication for definitive treatment but will likely prompt the need for repeat biopsies.

Review by 2030, subject to emerging evidence

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Benefits/desirable effects

Using size of effects based on thresholds of 1, 2 and 4 times the minimal clinically important difference (MCID) for small (MCID), moderate and large effects.

For men diagnosed localised prostate cancer **active surveillance based only on PSA testing** *when compared with immediate prostatectomy there was*

- **Small** (clinically important) increase in sexual quality of life at 2 years follow-up
- **Small** (clinically important) decrease in sexual bother at 2 years follow-up

when compared with immediate radiotherapy there was

- **Small** (clinically important) increase in bowel quality of life at 2 years follow-up

No clinically important benefits for other patient reported outcomes including urinary quality of life and urinary bother at 2 years

Harms/ undesirable effects

Using size of effects based on thresholds of 1, 2 and 4 times the minimal clinically important difference (MCID) for small (MCID), moderate and large effects.

For men diagnosed localised prostate cancer **active surveillance based only on PSA testing** *when compared with immediate prostatectomy or radiotherapy there was*

- **Small** (clinically important) increase in metastatic disease at 15 years follow-up
- **Small** (clinically important) increase in all-cause mortality at 15 years follow-up

No clinically important increases in prostate cancer mortality at 15 years or anxiety at 2 years

Balance of benefits and harms/ desirable and undesirable effects

For men diagnosed localised prostate cance**r, active surveillance based only on PSA testing** *when compared with immediate definitive therapy* both the benefits and harms are **small** but clinically important.

Certainty of the evidence

Very low

The certainty of the evidence was rated low or very low for each of the outcomes.

The low or very ratings were based on

- serious concerns about indirectness as almost all outcomes were derived from a RCT in which 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy
- serious, very serious or extremely concerns about imprecision: and/or
- serious concerns about the risk of bias due to lack of blinding and baseline variables not being accounted for in analyses for most quality of life outcomes.

Values and preferences

Substantial variability is expected or uncertain

Australian data (PCOR) show that sexual function at 12 months is still a significant concern for Australian men with localised disease *[55]*.

Expert opinion suggests that there will be variability in how men with localised prostate cancer value the outcomes of sexual, urinary and bowel quality of life at 2 years and the risk of metastases, overall mortality and prostate cancer mortality at 15 years.

As recommendations will be highly dependent on individual risk of disease progression risk group, an individualised approach is recommended in which shared decision making will be essential.

Resources and other considerations

Resources

Not considered as costs and resources were not included in the scope of these guidelines.

Acceptability - Substantial variability is expected or uncertain

The acceptability of active surveillance protocols will depend on the acceptability and frequency of the different modalities used to monitor for disease progression and the risk of disease progression.

Biopsy is a disincentive to active surveillance. Avoidance of biopsy is linked to lack of adherence to protocols.

RCTs comparing **annual biopsy protocols** ((NCT 0183265 and NCT 02564549) and PREFERE trial *[45]* in which active surveillance involved **biopsy at 6 months, 12 months and then every 3 years** were terminated early suggest these protocols were unacceptable to many patients.

In contrast the ProtecT trial ran for over 10 years suggesting that the active surveillance protocol used in this trial, **surveillance based only on PSA testing**, is likely acceptable to most men however in the era of MRI surveillance PSA surveillance is not that useful.

MRI is more acceptable than biopsy. In the Goteborg-2 trial screening participants reported MRI to be less bothersome than biopsy *[54]*.

Risk-stratified protocols are more tolerable.

Shared decision making and clear communications about the protocol are essential for the optimization of acceptability.

Some will experience psychological issues, potential to discuss options for counselling (practice point).

Feasibility - Important issues, or potential issues not investigated

There are no important barriers to active surveillance in Australia. Active surveillance is an accepted and established management option for men with localised disease in Australia.

Urologists in Australia have become more comfortable with active surveillance. They are more confident communicating what is involved and its benefits and recommending active surveillance as a management option for localised disease. This increase in confidence will likely alleviate the psychological burden associated with active surveillance felt by some individuals.

Rationale

Two RCTs were found that compared active surveillance with immediate definitive treatment for the management of localised prostate cancer. These were the ProtecT trial trial *[44]*, *[46]*,and the PREFERE trial *[45]*. The ProtecT trial provided the long-term clinical results and almost all of the patient reported outcome results. Starting in 1999 this trial used an active surveillance protocol in which PSA testing alone was used to monitor for disease progression. The PREFERE trial used PSA testing and frequent biopsies to monitor those on active surveillance and reported cancer-related quality of life results.

Neither trial provided results that could be used to identify optimal active surveillance protocols for men with localised prostate cancer. There was no clear evidence that benefits of the active surveillance protocols used in either trial outweighed any possible harms with neither trial providing quality evidence of benefits in quality of life that were clinically important. The PREFERE trial was unable to provide evidence as to any long-term harms as it was terminated early due poor recruitment and the ProtecT trial raised the possibility that active surveillance as practiced in that trial may increase the risk of metastatic disease.

Based on the uncertainty of the evidence, the possible harms of monitoring using only PSA testing to monitor for disease progression and the lack of clear evidence of clinically important quality of life benefits the working group was unable to recommend either of these protocols. Both protocols have been superseded in Australian clinical practice with the introduction of multiparametric MRI imaging of the prostate and MRI-targeted biopsies. The incorporation of multiparametric MRI imaging and targeted biopsies has given clinicians and patients greater confidence in choosing active surveillance resulting in its increasing uptake since 2016. As prostate cancer is usually a slowly progressing disease we did not find any comparative evidence of clinical outcomes for contemporary active surveillance protocols incorporating MRI imaging and targeted biopsies. In the absence of any evidence relevant to current clinical practice the working group developed consensus-based recommendations based on clinical expertise and experience.

No areas of major debate about the evidence and this recommendation were identified. This recommendation was reached with full consensus.

Clinical question/ PICO

Population: Individuals with biopsy-confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance with different monitoring protocols
Comparator: Immediate radical prostatectomy

Summary

Two RCTs were found that compared active surveillance with immediate prostatectomy for the management of localised prostate cancer. These were the ProtecT trial *[43][46]* protocol in which PSA screening alone was used to monitor for disease progression, and the PREFERE trial in which biopsies in addition to PSA testing were used to monitor for disease progression *[45]*. The ProtecT trial provided the long-term clinical results and almost all of the patient reported outcome results and the PREFERE trial reported cancer-related quality of life results.

There was no clear evidence that the active surveillance protocol used in the ProtecT trial achieved mortality results equivalent to those achieved by immediate prostatectomy. It is uncertain as to whether there was any clinically important difference in prostate cancer mortality between active surveillance and prostatectomy and whether there is a small increase in all cause deaths with active surveillance. Furthermore, there is a possibility that active surveillance as practised in this trial may increase the risk of metastatic disease.

For the quality-of-life related outcomes, either little difference is seen between active surveillance and immediate prostatectomy and/or it is uncertain as to whether there are small benefits with active surveillance.

For all outcomes the certainty of evidence was low to very low due to serious concerns regarding the imprecision, risk of bias and/or indirectness of the evidence to the clinical question. Most of the results were derived from the ProtecT trial in which it is likely that a substantial proportion of participants had non-localised disease at recruitment considering that 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Additionally, recruitment for the trial was carried out between 1999-2009 so it is likely that the Gleason scores for some of those recruited prior to 2005 would be different if determined today using the 2005 ISUP classification system.

More information can be found in the Technical Report.

Note: the evidence in this PECO informed consensus recommendations 8.2.1 and 8.2.2.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance with different monitoring protocols	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths - Active surveillance with PSA monitoring alone 15 years 9 Critical	Hazard ratio 1.52 (CI 95% 0.72 — 3.22) Based on data from 1,098 participants in 1 studies.	**22** per 1000 Difference:	**33** per 1000 **11 more per 1000** (CI 95% 6 fewer — 47 more)	**Very low** Downgraded by three levels due to very serious concerns re imprecision and serious concerns re indirectness	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 - Active surveillance based on PSA monitoring alone 15 years 8 Critical	Hazard ratio 1.12 (CI 95% 0.87 — 1.45) Based on data from 1,098 participants in 1 studies.	**212** per 1000 Difference:	**234** per 1000 **22.4 more per 1000** (CI 95% 25 fewer — 80 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness	We are uncertain as to whether active surveillance results in a clinically important (small)^ increase in prostate cancer mortality when compared with immediate prostatectomy.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance with different monitoring protocols	**Certainty of the evidence** (Quality of evidence)	**Summary**
Metastatic disease - Active surveillance with PSA monitoring alone 15 years 9 Critical	Hazard ratio 2.13 (CI 95% 1.32 — 3.45) Based on data from 1,098 participants in 1 studies.	**47** per 1000 Difference:	**97** per 1000 **50 more per 1000** (CI 95% 15 more — 106 more)	**Low** Downgraded by two levels due to serious concerns re imprecision and indirectness	Active surveillance may result in a clinically important (small)^^ increase in metastatic prostate cancer diagnoses when compared with immediate prostatectomy.
Sexual quality of life - Active surveillance with PSA monitoring alone 2 years 8 Critical	Measured by: EPIC sexual summary score Scale: 0 — 100 High better Based on data from 757 participants in 1 studies.	**33.4** (Mean) Difference:	**49.2** (Mean) **MD 14.8 higher** (CI 95% 11.2 higher — 18.4 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision	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 - Active surveillance with PSA monitoring alone 2 years 8 Critical	Measured by: EPIC sexual bother score Scale: 0 — 100 High better Based on data from 766 participants in 1 studies.	**47** (Mean) Difference:	**62.2** (Mean) **MD 15.2 higher** (CI 95% 10.3 higher — 20.1 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision	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 - Active surveillance with PSA monitoring alone 2 years 8 Critical	Measured by: EPIC bowel summary score Scale: 0 — 100 High better Based on data from 800 participants in 1 studies.	**93.8** (Mean) Difference:	**93.2** (Mean) **MD 0.6 lower** (CI 95% 1.8 lower — 0.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant difference in bowel quality of life when compared with immediate prostatectomy
Bowel bother - Active surveillance with PSA monitoring alone 2 years 8 Critical	Measured by: EPIC bowel bother score Scale: 0 — 100 High better Based on data from 800 participants in 1 studies.	**95.1** (Mean) Difference:	**94.2** (Mean) **MD 0.9 lower** (CI 95% 2.4 lower — 0.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in bowel bother when compared with immediate prostatectomy
Urinary quality of life - Active	Measured by: EPIC urinary summary score	**88.1**	**90.3**	**Low** Downgraded by	Active surveillance may result in a clinically

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance with different monitoring protocols	**Certainty of the evidence** (Quality of evidence)	**Summary**
surveillance with PSA monitoring alone 2 years 8 Critical	Scale: 0 — 100 High better Based on data from 794 participants in 1 studies.	(Mean) Difference:	(Mean) **MD 2.2 higher** (CI 95% 0.6 higher — 3.8 higher)	two levels due to serious concerns re risk of bias and indirectness	unimportant*^ difference in urinary quality of life when compared with immediate prostatectomy.
Urinary bother - Active surveillancewith PSA monitoring alone 2 years 8 Critical	Measured by: EPIC urinary bother score Scale: 0 — 100 High better Based on data from 790 participants in 1 studies.	**89** (Mean) Difference:	**88.6** (Mean) **MD 0.4 lower** (CI 95% 2.3 lower — 1.5 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant difference in urinary bother when compared with immediate prostatectomy
Anxiety - Active surveillance with PSA monitoring alone 2 years 8 Critical	Measured by: HADS anxiety sub score Scale: 0 — 21 Lower better Based on data from 942 participants in 1 studies.	**3.6** (Mean) Difference:	**3.9** (Mean) **MD 0.3 higher** (CI 95% 0.1 lower — 0.8 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active may result in a clinically unimportant*^ difference in anxiety when compared with immediate prostatectomy
Cancer-related quality of life - Active surveillance with PSA monitoring and biopsies at 6 and 12 months then every 3 years 2 years 8 Critical	Measured by: QLQ-C30 score Scale: 0 — 100 High better Based on data from 177 participants in 1 studies.	**75.3** (Mean) Difference:	**72.8** (Mean) **MD 2.5 lower** (CI 95% 12.7 lower — 7.7 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and imprecision	Active surveillance may result in a clinically unimportant*^ difference in cancer-related quality of life when compared with immediate prostatectomy
		^ 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			

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate radical prostatectomy	**Intervention** Active surveillance with different monitoring protocols	**Certainty of the evidence** (Quality of evidence)	**Summary**
		MCID and 4 x MCID for small (minimal clinically important difference), moderate and large effects			

Clinical question/ PICO

Population: Individuals with biopsy- confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance with PSA monitoring
Comparator: Immediate external beam radiotherapy

Summary

Evidence for this PICO was derived from a single randomised controlled trial, the ProtecT trial, in which active surveillance based only PSA level monitoring was compared with immediate prostatectomy or external beam radiotherapy *[44]*, *[46]*. When compared with immediate external beam radiotherapy (EBRT) there is a possibility that active surveillance based only PSA level monitoring may increase the risk of metastatic disease however it is uncertain as to whether there is no clinically important difference for the outcome of prostate specific cancer mortality or whether there is a small increase in all cause deaths with active surveillance. For the quality-of-life related outcomes, either little difference is seen between active surveillance and EBRT and/or it is uncertain as to whether there are small benefits with active surveillance.

For all outcomes the certainty of evidence was low to very low. There were serious concerns regarding the imprecision of effect estimates, risk of bias and indirectness. Major concerns regarding indirectness arose as it is likely that a substantial proportion of participants in this trial had non-localised disease at recruitment considering that 29% of those who underwent prostatectomy within 12 months of randomisation had pT3 or pT4 disease on prostatectomy. Additionally, recruitment for the trial was carried out between 1999-2009 so it is likely that the Gleason scores for some of those recruited prior to 2005 would be different if determined today using the 2005 ISUP classification system.

More information can be found in the Technical Report.

Note: the evidence in this PECO informed consensus recommendations 8.2.1 and 8.2.2.

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy	**Intervention** Active surveillance with PSA monitoring	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prostate cancer-specific deaths 15 years 9 Critical	Hazard ratio 1.14 (CI 95% 0.57 — 2.27) Based on data from 1,090 participants in 1 studies.	**29** per 1000 Difference:	**33** per 1000 **4 more per 1000** (CI 95% 12 fewer — 36 more)	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision and serious concerns re indirectness	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 years 8 Critical	Hazard ratio 1.14 (CI 95% 0.88 — 1.47) Based on data from 1,090 participants in 1 studies.	**211** per 1000 Difference:	**237** per 1000 **26 more per 1000** (CI 95% 23 fewer	**Very low** Downgraded by three levels due to extremely serious concerns re imprecision and	We are uncertain as to whether active surveillance results in a clinically important (small)^ increase in mortality when compared

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy	**Intervention** Active surveillance with PSA monitoring	**Certainty of the evidence** (Quality of evidence)	**Summary**
			— 83 more)	serious concerns re indirectness	with immediate radiotherapy.
Metastatic disease 15 years 9 Critical	Hazard ratio 2.08 (CI 95% 1.3 — 3.33) Based on data from 1,090 participants in 1 studies.	**50** per 1000 Difference:	**101** per 1000 **51 more per 1000** (CI 95% 15 more — 107 more)	**Low** Downgraded by two levels due to serious concerns re imprecision and indirectness	Active surveillance may result in a clinically important (small)^^ increase in metastatic prostate cancer diagnoses when compared with immediate radiotherapy.
Sexual quality of life 2 years 8 Critical	Measured by: EPIC sexual summary score Scale: 0 — 100 High better Based on data from 740 participants in 1 studies.	**43.4** (Mean) Difference:	**48.2** (Mean) **MD 4.8 higher** (CI 95% 1 higher — 8.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in sexual quality of life when compared with immediate radiotherapy
Sexual bother 2 years 8 Critical	Measured by: EPIC sexual bother score Scale: 0 — 100 High better Based on data from 744 participants in 1 studies.	**57.9** (Mean) Difference:	**61.2** (Mean) **MD 4.3 higher** (CI 95% 0.7 lower — 9.3 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in sexual bother when compared with immediate radiotherapy
Bowel quality of life 2 years 8 Critical	Measured by: EPIC bowel summary score Scale: 0 — 100 High better Based on data from 785 participants in 1 studies.	**89.3** (Mean) Difference:	**93.2** (Mean) **MD 3.9 higher** (CI 95% 2.3 higher — 5.5 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision.	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 2 years 8 Critical	Measured by: EPIC bowel bother score Scale: 0 — 100 High better Based on data from 789 participants in 1 studies.	**89.2** (Mean) Difference:	**94.2** (Mean) **MD 5 higher** (CI 95% 3 higher — 7 higher)	**Very low** Downgraded by three levels due to serious concerns re risk of bias, indirectness and imprecision	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 2 years 8 Critical	Measured by: EPIC urinary summary score Scale: 0 — 100 High better Based on data from 785 participants in 1 studies.	**91.4** (Mean) Difference:	**90.3** (Mean) **MD 1.1 lower** (CI 95% 2.6 lower — 0.4 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in urinary quality of life when compared with immediate radiotherapy

Outcome Timeframe	**Study results and measurements**	**Comparator** Immediate external beam radiotherapy	**Intervention** Active surveillance with PSA monitoring	**Certainty of the evidence** (Quality of evidence)	**Summary**
Urinary bother 2 years 8 Critical	Measured by: EPIC urinary bother score Scale: 0 — 100 High better Based on data from 781 participants in 1 studies.	**90.3** (Mean) Difference:	**88.6** (Mean) **MD 1.7 lower** (CI 95% 3.5 lower — 0.1 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in urinary bother when compared with immediate radiotherapy.
Anxiety 2 years 8 Critical	Measured by: HADS anxiety sub score Scale: 0 — 21 Lower better Based on data from 937 participants in 1 studies.	**3.7** (Mean) Difference:	**3.9** (Mean) **MD 0.2 higher** (CI 95% 0.2 lower — 0.6 higher)	**Low** Downgraded by two levels due to serious concerns re risk of bias and indirectness	Active surveillance may result in a clinically unimportant*^ difference in anxiety when compared with immediate radiotherapy.
		^ 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			

Clinical question/ PICO

Population: Individuals with biopsy-confirmed localised prostate cancer (cT1-2)
Intervention: Active surveillance
Comparator: Another active surveillance protocol

Summary

No randomised controlled trials were found that compared different active surveillance protocols.

More information can be found in the Technical Report.

Note: this PECO informed consensus recommendations 8.2.1 and 8.2.2.

Outcome Timeframe	**Study results and measurements**	**Comparator** Another active surveillance protocol	**Intervention** Active surveillance	**Certainty of the evidence** (Quality of evidence)
All outcomes including: All-cause mortality, Prostate cancer-specific mortality, Metastasis, Health-related quality of life and Adverse patient-reported outcomes		No eligible RCTs were identified. Five potentially relevant ongoing trials were identified by searches of clinical trial registries or literature searches, two of which were terminated early or withdrawn. More information can be found in the technical report here **[URL NEEDED]**		

Good practice statement

8.2.3 Avoid a change in treatment on an increase in PSA alone.

Perform repeat mpMRI preferably before repeat biopsy if PSA is increasing (PSA doubling time < 3 years).

Repeat biopsy may still have value even with an unchanged mpMRI.

Review by 2030, subject to emerging evidence

Good practice statement

8.2.4 Males with ultralow volume, low risk prostate cancer may be excused from more rigorous surveillance protocols.

Review by 2030, subject to emerging evidence

9. Watchful waiting

Watchful waiting is a conservative strategy for situations where treatment for prostate cancer is not immediately required, or the patient declines immediate intervention. As currently understood, it does not aim to cure prostate cancer, but to delay intervention until clinically warranted to prevent or relieve symptoms caused by the cancer. Watchful waiting involves avoiding treatment until there are symptoms or signs of progressive disease. Unlike active surveillance, a man on watchful waiting will generally not be offered potentially curative therapy if the cancer begins to grow. Treatment, when given, is directed towards slowing the disease's progression or relieving its symptoms, not to cure.

Watchful waiting in the context of a planned testing program for early detection of prostate cancer.

Although included in the 2016 Guidelines, the Review determined watchful waiting is not a primary management strategy in the context of a planned testing program for early detection of prostate cancer. Watchful waiting does, however, play a secondary role in harm minimisation (versus active surveillance) in that it decreases and at times, avoids overtreatment and associated treatment morbidities.

Good practice statement

9.1 The practice of watchful waiting is a patient-centred conservative strategy for managing prostate cancer when cure is not the goal. The aim is to maximise the patient's quality of life in alignment with their initial and evolving stated goals of care.

A comprehensive approach to managing prostate cancer involves the following general principles of monitoring and management options:

- Identify the patient's goals of care
- Tailor plans to the patient's wishes and needs
- Plan should include continuing clinical review, even if no investigations are to be done
- Ensure clear ongoing communication with the patient and their carers/families
- Allow for the possibility that the patient might want to change goals of care and approach to care.

Multidisciplinary management is recommended, involving the patient, primary health care and specialist settings, and other relevant health professionals.

Review by 2030, subject to emerging evidence

Practical info

The Review proposes the following considerations for health care professionals and men with prostate cancer:

- Watchful waiting is a strategy that focuses on patient-centered issues rather than primarily on cancer management. The intention of watchful waiting is to maximise the man's quality of life in alignment with their initial and evolving stated goals of care through:
  - Avoidance of immediate radical treatment of prostate cancer; and
  - Personalisation of investigations (scans and tests) and future interventions (treatments); and
  - Consideration of the patient's circumstances, including co-morbidities and other competing risks to the quality and duration of their life.
- Watchful waiting can be the treatment of choice for men with varying clinical diagnoses and a wide variety of personal priorities and preferences.

Other considerations

- No universal schedule is recommended for monitoring with blood tests or imaging.
- Investigations should be directed by clinical circumstances for those with co-morbidities, limited life expectancy, or expressed wish not to have treatment unless clinically indicated.
- Management should actively engage and involve other health care providers, particularly general practitioners and other primary health care professionals.
- Decisions should not be made on arbitrary criteria, such as age or a specific predicted survival period.
- Variations to the plan can be permitted without altering the overall intent (examples: patient request for PSA; specific investigation of and palliative radiation to a symptomatic lesion).
- Consider approaches to:
  - Reduce the risk of disease progression
  - Reduce the risk of requiring future treatment
  - Optimise the patient's ability to have future treatment, if appropriate
  - Provide supportive care and psychological support.
- Consider other investigations or interventions as required to improve quality of life or life expectancy. Examples (non-exhaustive list):
  - Prescribed exercise
  - Oncogeriatric referral if appropriate
  - Smoking cessation
  - Sun protection
  - Bone and metabolic health.
- Improved management of comorbidities, e.g., hypertension, diabetes, obesity, depression, and sexual dysfunction

Guiding framework for management of watchful waiting

Patient factors	Implications	Management points
Advanced or metastatic prostate cancer		
Otherwise well. Chooses watchful waiting instead of immediate active treatment.	Likely influenced by quality-of-life issues but need to understand each individual patient's reasons.	May choose future active treatment if required, depending on circumstances. If so: regular monitoring should be recommended, and an early exit plan agreed upon. If not: regular monitoring may be of less value. Other health interventions may be considered but prostate cancer outcomes are more likely to impact morbidity and mortality than in other settings above
Co-morbidities or otherwise limited life expectancy.	Prostate cancer treatment and outcomes are not high priorities for the man. Decision to have future treatment will depend on impact of the cancer relative to other issues.	May or may not choose or require treatment if develops advanced or metastatic disease. Frequency and nature of monitoring should be minimised. Concentrate on management of other issues.
Potentially curable localised prostate cancer for which other patients might choose treatment		
Otherwise well. Chooses watchful waiting instead of immediate active treatment.	Likely influenced by quality-of-life issues but need to understand each individual patient's reasons. Regular monitoring might be of greater value for the man.	May choose future active treatment if required, depending on circumstances. This in turn may mean that the man may choose to have some form of monitoring, regular or otherwise. "Teachable moment" for other health interventions.
Co-morbidities or otherwise limited life expectancy.	Prostate cancer treatment and outcomes are not high priorities for the patient. Decision to have future treatment will depend on impact of the cancer relative to other issues.	Unlikely to choose treatment if cancer remains localised. May or may not choose or require treatment if develops advanced or metastatic disease. Frequency and nature of monitoring should be minimised. Concentrate on management of other issues.
Localised low risk prostate cancer unlikely to require immediate treatment		
Otherwise well. Decides against active surveillance.	Low probability of negative impact on survival. Not the same as active surveillance. May be more likely to choose future active treatment if required.	Man may choose to have some form of monitoring, regular or otherwise, depending on willingness to choose active treatment later. "Teachable moment" for other health interventions.
Co-morbidities or otherwise limited life expectancy.	Prostate cancer treatment and outcomes are not high priorities for the patient.	Unlikely to choose treatment if cancer remains localised. Man may or may not choose or require treatment if develops advanced or metastatic disease.

Patient factors	Implications	Management points
	Decision to have future treatment will depend on impact of the cancer relative to other issues.	Frequency and nature of monitoring should be minimised. Concentrate on management of other issues.

Rationale

The Review determined that current definitions of watchful waiting *[256]*, *[63]*, *[64]*, *[138]*, *[3]* are not suitable in the context of a cancer management strategy for a planned testing program for early detection of prostate cancer. Rather watchful waiting is best defined as: a strategy that focuses on patient-centred issues rather than primarily on cancer management. Given this personalised approach to choosing watchful waiting adopted by the Review, a formal systematic review was precluded rendering the development of evidence-based guidelines based on PICOs unlikely to be possible or appropriate in the context of drafting guidelines and recommendations for watchful waiting. Instead, a guiding framework (below) and the above Good practice statement were developed through reviewing the 2016 Guidelines, considering national and international clinical practice changes, evaluating international guidelines and deliberations by a team of national experts recruited to the Expert Advisory Panel (EAP).

No areas of major debate about the evidence and this recommendation was identified. This recommendation was reached with full consensus.

Section F: Guideline implementation and monitoring

Considerations of guideline implementability, i.e., the characteristics that predict ease of and/or obstacles to implementation, is a critical factor in guideline development per the National Health and Medical Research Council (NHMRC) Procedures and Requirements for Meeting the NHMRC Standards for Clinical Practice Guidelines (NHMRC Guideline Standards *[75]*).

Poor implementation strategies result in guidelines that are not successful in improving care. Implementation failures can be both intrinsic (relating to the Guidelines themselves) or extrinsic (organisational/provider specific), therefore it is essential to identify factors that can affect implementability from the start of Guideline review, and strategise accordingly *[310]*.

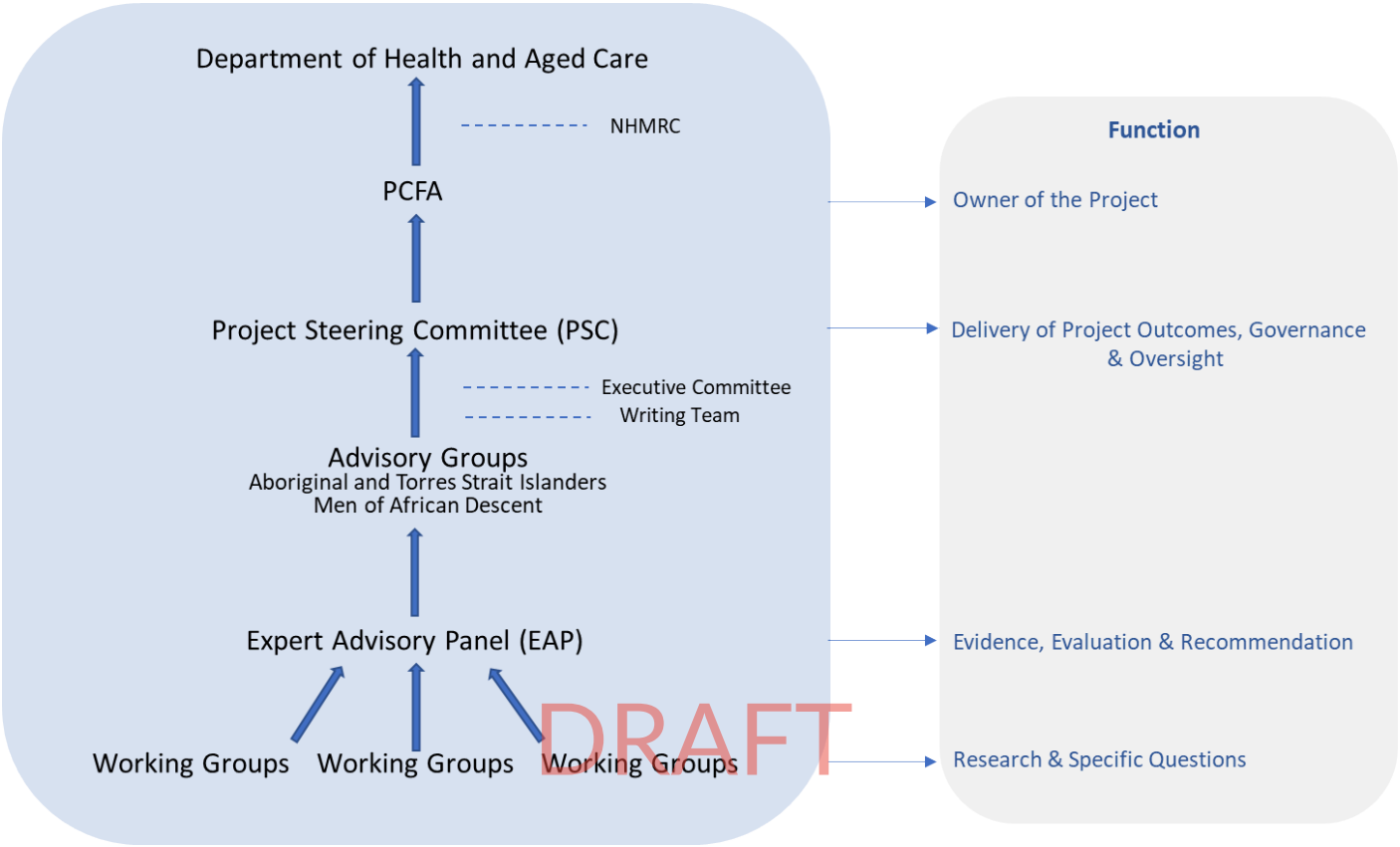
Hence, for the development of the DRAFT 2025 Guidelines, a dedicated Communications and Implementation Strategy Working Group was convened to co-ordinate the consultation, strategising and planning related to implementation and dissemination of the 2025 Guidelines and deliver the NHMRC mandated outputs related to implementation planning and dissemination of the 2025 Guidelines.

All information relating to Guideline implementation and monitoring, including the implementation planning approach and recommendations to best support implementability, can be found in the Dissemination report. Research priorities identified during the review and informed by public consultation can also be found in the Dissemination report.

Appendices

Appendix 1: Governance structure and group membership

Governance structure



Group membership

Project Steering Committee (PSC)

Member	Organisation
Prof. Jeff Dunn AO - Chair & CI	PCFA
Adj. Prof. Peter Heathcote – Co-Chair	Urologist & Chair of PCFA's Medical Advisory Committee
Prof. Mark Frydenberg AM - Urologist	Australian Urology Associates
Mr Mark Nevin	Cancer Council Australia
Prof. Vivienne Milch	Cancer Australia
Dr Weranja Ranasinghe	USANZ
Dr Brett Montgomery	RACGP
Dr Tanya Holt	RANZCR
Prof. Eric Chung	RACS
Assoc. Prof. Dr Ken Sikaris	RCPA
Prof. Karen Canfell	Daffodil Centre
Prof. Sue Evans	Cancer Registration
Adj. Assoc. Prof. Dr Peter Malouf	James Cook University (prev. Director and Assoc. Prof Indigenous Health Education Unit - Uni NSW)
Ms Gaye McPherson	Consumer Rep
Mr John Williams	Consumer Rep
Mr Andrei Norris	Consumer Rep
Ms Anne Savage	Ex Officio
Adj. Assoc. Prof. David Smith	Ex Officio
Past PSC Members	**Organisation**

Prof. Tanya Buchanan (Dec 2022 – Feb 2024)	Cancer Council Australia
Ms Megan Varlow (Feb 2024 – Feb 2025)	Cancer Council Australia
Adj. Assoc. Prof. Deanne Minniecon (Apr 2023 - July 2024)	First Nations Representative and Indigenous Peoples Health Adviser

Advisory Group Members

Member	Organisation
Mr Michael Adu Adjei	Consumer
Prof. Jeff Dunn AO	PCFA
Prof. Vanessa M. Hayes	Petre Chair of PC Research, Director, DoD HEROIC Prostate Cancer Precision Health Africa1K, Head of Ancestry & Health Genomics Laboratory, University of Sydney
Adj. Prof. Peter Heathcote – Co-Chair	Urologist & Chair of PCFA's Medical Advisory Committee
Mr Bill Hogan	Consumer
Dr Chris Ifediora	Associate Professor, Griffith University Medical School, Australia Founder and President, OCI Foundation Director, Cyfed Medical Group, Australia
Adj. Assoc. Prof. Peter Malouf	James Cook University (prev. Director and Assoc. Prof Indigenous Health Education Unit - Uni NSW)
Adj. Assoc. Prof. Deanne Minniecon	Faculty of Health, School of Exercise & Nutrition Sciences, Queensland University of Technology
Adj. Assoc. Prof. David Smith	The Daffodil Centre

Advisory Groups

Aboriginal & Torres Strait Islanders	Men of African Descent
Adj. Assoc. Prof. Deanne Minniecon - Chair	**Prof. Vanessa M. Hayes - Chair**
Adj. Assoc. Prof. Peter Malouf	Prof. Jeff Dunn AO
Mr Bill Hogan	Adj. Assoc. Prof. David Smith
Adj. Prof. Peter Heathcote	Adj. Prof. Peter Heathcote
Prof. Jeff Dunn	Mr Michael AduAdjei
Adj. Assoc. Prof. David Smith	Dr Chris Ifediora

Expert Advisory Panel (EAP)

Member	Organisation	Focus Area
Adj. Prof. Peter Heathcote – Chair	Urologist & Chair of PCFA's Medical Advisory Committee	Urology
Prof. Mark Frydenberg AM - Deputy Chair	Urologist - Australian Urology Associates	Urology
Prof. Vanessa M. Hayes	Petre Chair of PC Research, Director, DoD HEROIC Prostate Cancer Precision Health Africa1K, Head of Ancestry & Health Genomics Laboratory, University of Sydney	Risk Factors
Adj. Assoc. Prof. Jill Margo AM	Medical Writer, (prev. Health Editor - Financial Review)	Communications
Assoc. Prof. Nicole Heneka	Cancer Survivorship and Prostate Cancer Partnerships, Cancer Survivorship Research Group, Centre for Health Research. UniSQ	Communications Implementation
Ms Anne Savage	CEO, PCFA	Communications

Member	Organisation	Focus Area
		Implementation
Mr Mark Nevin	Cancer Council Australia	Communications
Mr Alan Barlee	Consumer	Consumer Advocacy
Mr Derek Lightfoot	Consumer	Consumer Advocacy
Mr Andrei Norris	Consumer	Consumer Advocacy
Mr John Williams	Consumer	Consumer Advocacy
Mr Andrew Blackwell	Consumer	Consumer Advocacy
Mr Greg McRoberts	Consumer	Consumer Advocacy
Dr Gary Morrison	Consumer	Consumer Advocacy
Assoc. Prof. Michael O'Callaghan	Executive Officer - SA PC Clinical Outcomes Collaborative	Epidemiology
Prof. Peter Baade	Senior Manager, Descriptive Epidemiology - Cancer Council QLD	Epidemiology
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Appendix 2: Clinical questions and PICOs/PECOs

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?
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?

Clinical Question (CQ)	PICO or PECO
	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?
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?
CQ 10 What should be the criteria for choosing active surveillance in preference to definitive treatment	**PICO 10A and 10A (subgroups)** For individuals with biopsy-diagnosed localised prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does

Clinical Question (CQ)	PICO or PECO
to offer as primary management to individuals who have a positive prostate biopsy?	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?

[i] *Population, Intervention, Comparator, and Outcomes*

[ii] *Population, Exposure, Comparator, and Outcomes*

[iii] *Systematic review not undertaken*

Appendix 3: Literature reviews

Men of African descent Advisory Group report

Prostate cancer is the leading cause of cancer death in many Black males of sub-Saharan ancestry. Little is known about the risk of diagnosis or death in males of Black sub-Saharan ancestry resident in Australia. In order to develop appropriate Australian based recommendations regarding early detection of prostate cancer in this population, we investigated international epidemiological patterns of prostate cancer and specific recommendations regarding early detection in black males of sub-Saharan ancestry.

Background

Prostate cancer mortality rates are highest in the Caribbean, followed by the sub-Saharan Africa. A 2020 Lancet publication on cancer risk in the sub-Saharan Africa, reported that prostate cancer was the leading incident cancer in 49 countries and the leading cause of cancer death in 26 of those countries*[26]*. Black males of sub-Saharan ancestry are at higher risk of being diagnosed with prostate cancer and dying from it in Africa, as well as in those who have migrated to other parts of the world such as the United States, United Kingdom and in the Caribbean.

Are males of African ancestry genetically predisposed to increased risk of prostate cancer?

As a leading cause of cancer-related deaths in sub-Saharan Africa, prostate cancer mortality rates are highest in southern Africa (29.7 age-standardised rate per 100,000 males) and east Africa ranking fifth (16.8 per 100,000) *[26]*. A study of 1387 Black African men from the multi-ethnic Southern African Prostate Cancer Study (SAPCS) showed that poverty is a decisive factor for disease grade and age at diagnosis *[27]*.

The first prostate cancer whole genome data generated for the SAPCS study for sub-Sharan Africa reported that *[28]*:

- Black African men have a 2.1 fold and a 4.8 fold increased risk of being diagnosed with more advanced prostate cancer and PSA levels

associated with high risk disease, respectively, than Black American men, and this risk is greater in rural men *[30]*, *[29]*.
- Genomic based disparities extend across sub-Saharan African populations.

Males of Black sub-Saharan ancestry have a higher incidence of aggressive prostate cancer and prostate cancer mortality, compared with white individuals *[178]*, *[244]*, *[261]*. They are also more likely to be diagnosed with more advanced disease and have increased risk of metastatic disease *[235]*, *[339]*, *[243]*. The most recent evidence[158] from a retrospective study in almost 8,000 self-identified African men diagnosed with prostate cancer reported that Kenyan and South African men presented with significantly more aggressive disease, as defined by ISUP grade groups 4 and 5 (59% vs. 41%) and PSA >20 µg/L (67% vs. 44%). Compared with period-matched, non-African US-SEER data, Southern and East African Kenyans presented with more advanced disease and PSA >20 µg/L (50% vs. 10%). Irrespective of country of origin, over a quarter of African men presented with PSA levels >20 µg/L.

International data

United States of America (USA)

There are approximately 42 million Americans who identify as black, making up 12% of the total population *[31]*. Most of the evidence regarding cancer risks associated with African ancestry is derived from the USA. This shows the risk of prostate cancer incidence and mortality is greatest in African American males compared to males from other racial or ethnic groups *[31]*. African American males are diagnosed with prostate cancer at a younger age compared to males from other ethnic groups *[31]*. A systematic review of 52 studies concluded that men of Black African ancestry in the USA have approximately 1.8 times higher population level incidence rates compared with White males *[32]*. Selection bias, often driven by socioeconomic factors, even for studies within black communities, may under-estimate the actual risk in the average black patient in the USA *[33]*.

Findings from three randomised controlled trials (RCTs) provided evidence that Prostate Specific Antigen (PSA) testing for males aged between 50 and 70 years of average prostate cancer risk, reduced the risk of diagnosis of metastatic disease and risk of prostate cancer deaths. However, the evidence specifically for Black men is lacking *[212]*, *[183]*, *[159]* *[134]*. A recent study of 75,000 black and 200,000 white US Veterans, after having controlled for SES factors and healthcare access, showed that Black men have double the risk at of being diagnosed with prostate cancer a younger age, and with more aggressive disease, than white men *[34]*.

Given the disparity in prostate cancer mortality, the US Prostate Cancer Foundation issued clinical PSA screening guidelines for Black men *[9]*, recommending:

- *"For Black men who elect screening, a baseline PSA test should be done between the ages of 40 – 45. Depending on the PSA value and the individual's health status, annual PSA screening should be strongly considered"*
- *"Black men with an even higher risk of prostate cancer due to a strong family history and/or known carriers of high-risk genetic variants should consider initiating annual PSA screening as early as age 40."*

The US Preventative Services Task Force (USPSTF) recommendations discuss racial disparities in prostate cancer outcomes but do not currently provide any specific guidance for Black men *[193]*. These guidelines are currently under review.

Canada

The total population of those of African ancestry in Canada is far smaller than the USA. According to the 2006 Canadian Census of Population, approximately 4.3% of the Canadian population is of African ancestry *[91]*, compared to13.7% in the USA *[92]*. Interestingly, the increased risk of prostate cancer incidence and mortality seen in the USA was not apparent in Black African-Canadian males probably due to lesser socioeconomic disparity *[35]*.

Assessment by socioeconomic status (SES) showed that the rates of prostate cancer diagnosis as well as mortality rates were significantly lower in the SES quintile with the highest percentage of Black African–Canadian males compared to that with the lowest percentage (IRR-Black Q5 vs. Q1 = 0.73; 95% CI 0.72–0.74) (Mortality: Q5 vs Q1 0.65 (0.62-0.68). Likewise, the Canadian Black males also had similar diagnostic PSA levels, TNM categories and Gleason grade groups as men of other races. It was however noted that men who identified as black were diagnosed with prostate cancer at an earlier age compared to men of other races *[36]*.

Canadian men who identified as Black had similar rates of prostate cancer–specific survival (hazard ratio [HR], 1.10; 95% CI, 0.41-2.97), metastasis-free survival (HR, 0.88; 95% CI, 0.42-1.46), and overall survival (HR, 0.55; 95% CI, 0.25-1.24), as males of other races *[36]*.

In summary, Black men In Canada, despite being diagnosed at a younger age, experience comparable prostate cancer outcomes compared with males of other races. The Canadian Cancer Society recommends that Black males aged in their 40s should consider discussing with their healthcare provider, in making an informed decision about PSA testing. Current Canadian guidelines on PSA testing do not provide specific advice regarding Black males *[281]*, *[264]*.

United Kingdom (UK)

The PROCESS Cohort Study published in 2008, was a cross-sectional study of first-generation black Caribbean and black African men in the United Kingdom *[128]*. It showed:

- Black men had higher age-adjusted rates of prostate cancer (166 per 100,000, 95% confidence interval [95%CI], 151–180 per 100,000) than white men (56.4 per 100,000, 95%CI, 53.3–59.5 per 100,000).
- The relative risks for all black, black Caribbean, and black African men were 3.09 (95%CI, 2.79–3.43), 3.19 (95%CI, 2.85–3.56) and 2.87

(95%CI, 2.34–3.53), respectively.
- There was no strong evidence that the rates for black Caribbean differed from Black African men.
- The higher risk in Black men compared with white men was more apparent in younger age groups (p value for interaction <0.001).

The Prostate Cancer Foundation UK recommends that Black men talk to their GP about a regular PSA blood test from the age of 45. Raising awareness of prostate cancer amongst Black communities is currently underway in the UK *[39]*.

Caribbean/Central America

The Caribbean has one of the highest prostate cancer mortality rates in the world, but no reliable race specific information is available. Like all other regions, age appears to be a significant factor where the age-specific prostate cancer incidence rates increased from 6.0 (95% confidence interval: 1.6–15.3) per 100,000 men at ages 40 to 44 years to 1,026.6 (95% CI: 898.8–1,167.6) per 100,000 in men aged 70 to 74 years, and declined thereafter *[38]*. In 2020, the International Agency for Research on Cancer estimated the ASR incidence of 75.8 cases per 100,000 people, whereas the mortality was 27.9 cases per 100,000 people *[31]*.

There is universal health care in the Caribbean, however disparities in socio-economic and healthcare access are highly prevalent.

Australian data

Australia has a growing African diaspora. Approximately 437,000 people of African origin were living in Australia in 2023. The median age of African migrants residing in Australia is 43, compared to Australian born median age of 34 *[104]*.

Australian immigration data since 2010, indicates that the proportion of migrant arrivals from the sub-Saharan regions, which includes South Africa, is relatively small, compared to the other migrant groups, although these numbers are increasing *[88]*. There was a total of 737,200 overseas migrant arrivals in Australia in 2023, with 27,070 from the sub-Saharan regions. Of these 39% were from South Africa (n=10590), while the remaining were mainly from Kenya, Zimbabwe, Nigeria, Mauritius, Ghana, Ethiopia, Zambia, and Somalia where prostate cancer rates in their homeland are high *[88]*.

The limited body of evidence related to prostate cancer in African migrants in Australia is largely related to South African migrants *[104]*. A NSW report on cancer by country of birth (Cancer incidence in NSW migrants 1991-2001) reported that the prostate cancer incidence in South Africans was similar to that of Australian born men *[321]*. However, it is noted that a large proportion of South African migrants are not of black sub-Saharan ancestry. A more recent publication from NSW indicated a significantly lower rate of diagnosis of prostate cancer in men from South-East Africa *[41]*.

Summary

Black sub-Saharan African ancestry is a known risk factor for the detection of clinically significant prostate cancer and prostate cancer mortality, however there is lack of evidence for this population in Australia. Hence the recommendation for this population for the early detection of prostate cancer in Australia is based on international evidence and clinical practice.

Recommendations

- Males with Black sub-Saharan ancestry from age 40-69 years should consider:
  - beginning shared decision making about PSA testing; and
  - re-testing every two years.
- For men with Black sub-Saharan ancestry aged between 40-49 years:
  - follow-up testing should be considered every 2 years for PSA levels ≤2 µg/L; and
  - annual testing should be considered for levels >2 µg/L.
- For men with Black sub-Saharan ancestry aged between 50-69 years:
  - follow-up testing should be considered every 2-years for those with PSA levels ≤3 µg/L; and
  - annual testing should be considered for levels >3 µg/L.
- Individuals with Black sub-Saharan ancestry aged over 70 years should:
  - discuss with their health care provider about whether to have a PSA test; and
    - be encouraged to make an informed and shared decision based on their age, life expectancy, health status, family history, and prior PSA levels.
- Individuals with Black sub-Saharan ancestry aged over 70 with less than 7 years life expectancy should not be offered a PSA test.
- Individuals with Black sub-Saharan ancestry with an additional risk of prostate cancer (i.e., family history and/or known carriers of high-risk genetic variants) should consider initiating annual PSA screening from age 40 as there is currently no evidence to suggest benefits of testing any earlier. Future research should consider addressing this caveat.
- Review these recommendations in three years.

Rationale

- Individuals of Black African ancestry have ~ two-fold higher risk of being diagnosed with prostate cancer before the age of 45 than

Whites *[286]*, *[219]*, *[249]*.
- Individuals of Black African ancestry have a higher incidence of aggressive prostate cancer and prostate cancer mortality, compared with white individuals *[244]*, *[261]*, *[178]*. Black individuals are also more likely to be diagnosed with more advanced disease, thus have increased risk of metastatic disease *[235]*, *[339]*, *[243]*.
- Australia has a growing African diaspora. The median age of sub-Saharan migrants living in Australia is 43 years *[88]*, thus early detection using PSA testing and intervention for asymptomatic men at highest risk of high-risk disease is unlikely to have a large impact on resources in the short term, but has the potential to reduce future prostate cancer deaths as this cohort ages.
-

Considerations for Communications & Implementation Strategy Working Group

- Clear and concise information, co-designed and tailored to this community regarding shared decision making is necessary.
- Information channels should engage with the active community networks and appropriate media

Social determinants of prostate cancer and early detection of prostate cancer in Australia

This section reviews the evidence for socio-demographic factors contributing to health inequities in prostate cancer detection and outcomes. It addresses potential differences in access to, and understanding of, prostate-specific antigen (PSA) testing, treatment, and outcomes among Australian priority populations. These populations include Aboriginal and Torres Strait Islander peoples, primary care providers, migrant groups, culturally and linguistically diverse (CALD) communities—notably those of African ancestry—the LGBTIQA+ populations, individuals with disabilities, and residents of rural and remote areas. Factors that may differentially affect users of public versus private healthcare services, prisoners, military veterans, and firefighters are also examined. Ultimately, this section highlights the gaps and barriers hindering early detection and management of prostate cancer, which may lead to inequitable outcomes for affected individuals. It concludes with recommendations for equitable access to guidelines and identifies future research priorities to address these disparities.

Background

Socio-demographic characteristics are well established determinants of both access to health services and health outcomes *[226]*. Populations known to have less advantages, and those experiencing lower socio-economic status and poorer health literacy tend to have lower life expectancy, higher rates of illness and higher risk of disability and death *[119]*. Prostate cancer is the most commonly diagnosed cancer in Australia, with both prevalence and the number of deaths expected to increase in the future *[120]*, *[142]*. There is some evidence that specific priority groups experience worse prostate cancer outcomes than the population as a whole in Australia. The most comprehensively reported area of inequity in prostate cancer incidence and mortality shows consistently higher mortality rates in residents from regional and rural areas compared to those from major cities *[351]*. These disparities may be influenced by differences healthcare access and other underlying socioeconomic factors *[181]*.

There is limited evidence on differences in PSA testing participation by area based socio-economic factors *[226]*. While Australia has never implemented a formal systematic prostate cancer screening program, the PSA test is widely used among individuals, and more so in those residing in major cities, and those with higher levels of education and private health insurance *[148]*, *[255]*, *[98]*. The ad-hoc use of PSA testing, generally in those of higher literacy and greater socio-economic status has, in other countries, been attributed to driving and increasing the inequities in outcomes between socio demographic groups *[336]*.

The Australian Cancer Atlas reported a 26% participation rate in PSA testing in men aged 50-69 in a two-year period between 2017-18 *[226]*, *[403]*. However, PSA testing rates varied by area of residence, likely reflecting similar disparities in incidence patterns *[226]*. Specifically, prostate cancer incidence rates were lower in regional and rural areas, as well as in socioeconomically disadvantaged communities. The extent to which geographical patterns of testing vary according to other socio-demographic characteristics of the populations e.g. Aboriginal and Torres Strait Islander people or culturally and linguistically diverse (CALD) communities is not clear. It is however known that Aboriginal and Torres Strait Islander communities are more likely to reside in rural and remote regions *[96]*, *[118]*. Similarly, men living in inner regional, rural, or disadvantaged areas are more likely to be diagnosed with advanced disease and thus face a higher risk of progression to metastatic prostate cancer *[240]*.

Equity issues, such as low levels of community awareness, low health literacy, and travel-related barriers to health care all likely impact access to early detection and treatment. Low health literacy, coupled with the sub-optimal readability and understandability of some available prostate cancer information, may hinder individuals informed decision making and participation in testing and treatment *[314]*.

Our knowledge on socio-demographic differences in PSA testing and prostate cancer is limited and often based on outdated population estimates, underscoring the need to update and improve both evidence for priority populations *[96]*, *[277]*. Addressing disparities involves identifying specific needs, providing clear information and culturally appropriate communications and increasing access to diagnostic and treatment services for diverse and underserved groups. In the implementation of updated Guidelines on the early detection of prostate cancer these specific aspects need to be considered to ensure some of the previous and currently described inequities are not further compounded.

Methods

Guideline Review Group

A panel was formed to consider social determinants and equity issues in the review of Australian Guidelines on prostate specific antigen testing. The panel included consumers, general practitioners, clinicians, researchers, health economists, and policymakers. A specific working group was convened to address socio-demographic implications of early detection of prostate cancer. A framework focused on equity issues in early prostate cancer detection was developed, guiding the identification of socio-economically disadvantaged (priority) populations and highlighting their specific challenges. The working group discussed and documented key concerns regarding access to PSA testing and implications for future research priorities.

Search Strategy

A narrative review was conducted to identify the epidemiology, barriers and health inequities faced by Australians in accessing PSA testing and care. An electronic search was performed across databases and search engines, including PubMed, Medline Ovid, Google, and Google Scholar, to gather relevant sources from January 2010 to July 2024. Key search terms were informed by existing studies on prostate cancer inequities and MeSH terms from PubMed. Additionally, reference lists from included sources were manually searched and used to identify other relevant sources. Key terms including "prostate cancer," "testing," "diagnosis," "disadvantages", "disparities," "barriers," and "inequities" guided the search for relevant sources. Australian-based sources that discussed inequities in priority populations were included.

Terms and definitions

Search terms related to the Aboriginal and Torres Strait Islander peoples and Australian individuals with African ancestry were included in the systematic reviews for individual questions for this review (see Technical Report accompanying these Guidelines).

Geographical factors

National trends in testing, incidence and mortality

Australia has consistently had one of the highest incidence rates of prostate cancer internationally *[31]*. In 2019, prostate cancer accounted for 25% of all cancers diagnosed in Australian men *[229]*, *[116]*. The age-standardized incidence rate increased significantly, from 80 per 100,000 in 1982 to 151 per 100,000 in 2022, reflecting a 144% rise between 1982 and 2009 *[142]*, *[174]*. The introduction of PSA testing in Australia led to an increase in incidence rates *[120]*. The number of prostate cancer cases rose from 3,606 in 1982 to 26,400 in 2024 *[120]*, *[166]*. Increased incidence rates following the introduction of PSA testing as a relatable item on the Medicare Benefit Schedule can be attributed to greater awareness, more testing, and changes in diagnostic criteria *[266]*. Mortality rates increased in the early 1980s but have declined significantly over the past four decades, with a nearly 13% reduction from 1982 to 2020 *[142]*. The age-standardized mortality rate fell from 35 per 100,000 in 1982 to 22 per 100,000 in 2020.

Patterns of testing, incidence and mortality by region of residence

PSA testing rates differ significantly among various Australian demographic groups. Men residing in urban areas, those with higher education levels and private health insurance have been shown to be more likely to participate in PSA testing *[269]*.

In rural and remote areas, the rate of PSA testing has consistently been lower than in urban areas. In 2008-09, the testing rate for men aged 50–79 was 21,267 per 100,000 in rural areas, compared to 24,606 per 100,000 in urban areas *[123]*. In 2011, both PSA testing and radical prostatectomy rates were lower in rural areas.

The national five-year relative survival rates for those diagnosed with prostate cancer increased from 58.4% in 1981–1985 to 91.3% in 2011–2015 *[239]*. More recent publications have shown that survival rates differ by region; for example, in 2020, the Australian Cancer Atlas showed considerable geographic variation in survival, with 78% five-year survival in Southwest Victoria, compared to the national average of 95% *[403]*, *[239]*. Men residing in low SES areas had a 34%-40% greater risk of dying from the disease *[351]*. Men living outside major cities had a 24% higher likelihood of dying within five years of diagnosis of prostate cancer compared to those in urban areas *[351]*. Prostate cancer incidence and mortality rates are typically higher in rural areas than in urban areas, attributed to poorer health outcomes, health literacy, and possibly differences in testing behaviours *[148]*. Notably, between 2005 and 2009, there was significant variability in sociodemographic factors and a pronounced decline in PSA testing rates as distance from major cities increased*[139]*.

Individuals living in rural Australia are more likely to be diagnosed with advanced-stage prostate cancer *[351]*, *[216]*, *[227]*. Despite significant efforts to address poorer survival in rural Australia the survival disparity between rural and urban areas remains, with no significant reduction in this gap over time *[351]*. Geographic variations in prostate cancer care are influenced by factors including a scarcity of local healthcare providers, limited diagnostic services, inconsistent detection methods and long travel distances for care and treatment. *[181]*, *[229]*, *[227]*' *[218]*. Men in regional and remote areas are 2.5 to 6 times more likely to have difficulty accessing a local GP compared to urban residents, which has been attributed to lead to later-stage diagnoses and poorer outcomes *[351]*, *[227]*.

The variation in patterns of PSA testing by geographic region have been documented, but the extent to which this relates to mortality outcomes is unknown.[203] It is important to ensure that all Australians, irrespective of their area of residence, have the same level of access to shared decision making regarding early detection.

Socio-economic status

Socioeconomic status (SES) is a composite measure that reflects an individual's or group's economic and social position relative to others *[108]*. This is generally based on factors such as income, education, and occupation. SES is often used to highlight economic disparities within society and is a key determinant in various social outcomes, including education and access to social and material resources. In Australia descriptions

of health outcomes often define groups by the areas in which they reside and categorise these by the ABS developed SEIFA (Socio-Economic Indexes for Areas) index *[108]*, *[109]*. SEIFA is a suite of indexes created used to rank areas in Australia according to issues such as relative socio-economic advantage and disadvantage.

In Australia, men living in major cities, and those from most advantaged areas have consistently had higher rates of PSA testing than the general population *[148]*, *[109]*. Low socioeconomic status has been associated with a higher occurrence of advanced prostate cancer at diagnosis and greater mortality *[220]*. A population-based study using Medicare data for nearly three million Australian men with records of PSA testing found consistent testing patterns across all socioeconomic groups *[227]*. This study suggested that factors acting at the national level, such as clinical practice guidelines, influence patterns of testing more than local factors. Additionally, previously documented disparities in PSA testing based on socioeconomic status have decreased within the past decade.

From 2012-2016, the age-standardised incidence rates of prostate cancer were lower in the lowest socioeconomic areas (137 cases per 100,000 people) compared to higher socioeconomic areas (169 cases per 100,000 people) *[117]*. In contrast, the age-standardised mortality rates, between 2015-2019, were higher in most disadvantaged areas (27 deaths per 100,000 people) and lower in the least disadvantaged areas (22 deaths per 100,000 people). Additionally, prostate cancer mortality rates have remained consistent across broad socio-economic groups, although men in affluent areas generally have lower other-cause mortality *[326]*.

Primary care providers

Recent studies have explored General Practitioners (GPs) knowledge on PSA testing, communication approaches, and accessibility, particularly in rural and remote areas *[218]*, *[223]*. A qualitative study found differences in the PSA testing process between metropolitan and regional areas *[218]*. Men in metropolitan areas could complete testing within 10 days, while those in regional areas faced waiting periods of up to a month for a doctor's appointment and three to six months for results. Additionally, another qualitative study found that GPs' knowledge of prostate cancer care is not aligned with the latest evidence *[148]*. In this study, GPs noted a lack of consensus on PSA testing, promoting the need for more clear guidance around testing. Other factors contributing to poor prostate cancer care in regional areas include limited access to specialists, diagnostic equipment, and operating rooms *[295]*.

Aboriginal and Torres Strait Islander Peoples

Early detection of prostate cancer in Aboriginal and Torres Strait Islander Peoples is covered in the following sections:

- Section C: Priority populations - 3.1 Aboriginal and Torres Strait Islander males
- Appendix 3: Literature reviews - Aboriginal and Torres Strait Islander populations advisory group report

Migrant groups

Migrant status is often associated with risk of both incidence and mortality of cancer. Baseline risks associated with genetics, background exposures or differences in lifestyle can account for some of these observations *[41]*. Differences in risk can often attenuate over time as migrant groups acculturate to the country in which they have moved. In Australia, migrant groups have traditionally experienced a lower risk of diagnosis of prostate cancer than Australian born residents. Furthermore, men of African ancestry, as well as culturally and linguistically diverse populations, are often characterised within the migrant group. For this report, both populations (CALD in general and also men of African ancestry) are considered as important sub-groups of the larger migrant populations.

PSA testing in migrant groups

A 2023 population-based study suggested a link between incidence patterns in Australian migrants and the prevalence of PSA testing, although findings from New South Wales were inconsistent *[41]*. The CHAMP study, conducted from 2005 to 2007, found that Australian-born men had the highest rate of PSA testing at 53%, compared to those born in Italy (44%), the UK (43%), Ireland (43%), and Greece (46%) *[237]*. In contrast, Australian men born in China (34%) had the lowest likelihood of receiving PSA testing. Additionally, migrants from Vietnam (IRR = 0.32, 95% CI 0.29–0.35) and China (IRR = 0.38, 95% CI 0.35–0.41) had the lowest PSA testing rates *[41]*. However, analysis of linked Medicare data from January 1, 2012, to December 31, 2014, revealed only minor differences in PSA testing among major migrant groups. Other studies based on self-reporting found that urban East Asian males and Chinese-born males testing rates were 30% and 50% lower, respectively, compared to Australian-born males *[41]*, *[237]*, *[340]*, *[341]*.

This discrepancy may be attributed to higher testing rates within certain migrant populations or challenges related to health literacy and the uncertainty around the accuracy of self-reported testing behaviours among non-English speaking migrants *[255]*.

Refugee and migrant men living in regional regions are more likely to have undergone a PSA test compared to those in urban areas *[341]*. Several factors may influence testing decisions, such as increased promotion of testing in regional areas, stronger community engagement that may also relate to acculturation.

Incidence and mortality in migrant groups

Data from the Australian Cancer Database (2005–2014) noted that, except for migrants from New Zealand, Ireland, and Melanesia—who have similar incidence rates to Australian-born men—other migrant groups had lower prostate cancer incidence rates *[41]*.

Residents born outside Australia, especially those from North-East Asia (IRR = 0.40, 95% CI 0.38–0.43), had a lower incidence and mortality rates of prostate cancer compared to residents from English speaking countries *[41]*, *[184]*. In 2012, age-standardised prostate cancer mortality

rates by country of birth are as follows: Northern Europe (14.5 per 100,000), Australia/New Zealand (12.9 per 100,000), Northern Africa (7.0 per 100,000), and Asia (3.8 per 100,000) *[200]*. Therefore, individuals born in Asia and North Africa have the lowest prostate cancer mortality rates. These differences in survival rates likely reflect a combination of events, as studies from New South Wales suggest that geographic variations in patient management, access to follow-up services, and socioeconomic factors can all contribute to variations in outcomes *[351]*, *[175]*.

CALD communities

In the Australian context, "culturally and linguistically diverse" (CALD) describes populations distinct from the majority Anglo-Celtic culture *[171]*. This includes individuals and communities with varied cultural, religious, and linguistic backgrounds who migrate to Australia, bringing diverse values, beliefs, and perspectives. Individuals from these groups communicate exclusively in languages other than English or alongside English *[260]*. CALD communities can be viewed as a subset of migrant communities with higher levels of need. Despite Australia's status as one of the most culturally diverse countries globally, individuals from these communities often encounter significant challenges in navigating the health and welfare system *[118]*. Although individuals from these communities are reported to be less likely to be diagnosed with prostate cancer compared to Australian-born men—suggesting a lower incidence of the disease among CALD groups—15% of prostate cancer cases in 2014 were among men from these communities *[276]*. Prostate cancer ranks as the second most major health issue among Arabic, Greek, and Italian speakers and the third among Vietnamese speakers *[276]*.

There is limited understanding of the specific prostate cancer information and support needs within the CALD community *[276]*.The lack of accessible and culturally appropriate multilingual information and resources may deter CALD individuals from undergoing early detection and informed decision making for procedures such as PSA tests. Furthermore, language barriers and religious beliefs can hinder access to health information on testing, treatment and health services, resulting in inadequate care *[276]*.

Cultural differences can significantly affect how individuals interact with health services. [221] For example, in Chinese society, a prostate cancer diagnosis may commonly be seen as a sexual issue, making discussions with female family members, health professionals, or friends uncomfortable *[276]*. Therefore, it is crucial to encourage CALD individuals to comfortably discuss prostate cancer with others. Additionally, there appears to be insufficient publicity about prostate cancer within ethnic communities, such as limited coverage on ethnic media.

Non-English-speaking migrants often face challenges in health literacy and language barriers, which impact their clinical decision making and outcomes *[148]*, *[200]*. Various cancer organizations have released resources on prostate cancer care for common languages in Australia. The Cancer Institute NSW provides materials covering all aspects of prostate cancer in eight languages, including Arabic, Chinese, and Italian *[146]*. Meanwhile, Cancer Council Australia and PCFA provide resources in eleven and eight languages, respectively, with six languages overlapping with those from the Cancer Institute NSW *[144]*, *[275]*.

To address some of the barriers described above, translated materials should be distributed to medical practices surrounding CALD communities, community groups, and ethnic radio.[189] Furthermore, increasing publicity about prostate cancer in these communities could enhance awareness and access to information on PSA testing.

Black males of sub-Saharan ancestry

Early detection of prostate cancer in black males of sub-Saharan ancestry is covered in the following sections:

- Section A: Risk assessment - 1.2 Black males of sub-Saharan African ancestry living in Australia
- Appendix 3: Literature reviews - Men of African descent advisory group report

LGBTIQA+ community

There is little evidence in Australia and few studies internationally on differences in PSA testing in gender diverse communities. A US survey reported lower rates of PSA testing in homosexual men compared to heterosexual men *[205]*. Research shows that experiences of prostate cancer treatment differ significantly between heterosexual and LGBTIQA+ members, the findings show that androgens influence sexual motivation, arousal, and behaviour differently according to sexual orientation. Specifically, treatment with an anti-androgen in men undergoing prostate cancer therapy demonstrated significant differences in sexual experiences between heterosexual and homosexual men *[253]*. Sexual minorities, gay, bisexual, and queer men often face greater challenges with erectile and orgasmic function and reduced libido compared to their heterosexual counterparts *[253]*, *[252]*, *[329]*. These men are also more likely to undergo prostatectomy due to the hetero-centric nature of the healthcare system, which often assumes heterosexuality and requires LGBTIQA+ members to consistently disclose their identities to healthcare providers. Thereby, making them feel like a 'hidden' population *[252]*, *[328]*. Moreover, lack of knowledge and prejudice among healthcare professionals can hinder the care of LGBTIQA+ individuals, potentially delaying early diagnosis and treatment *[153]*.

Data on Australian gay and bisexual men's prostate cancer experiences is also limited *[221]*. Members of the LGBTIQA+ community face unique challenges in prostate cancer detection and care, including stigma, discrimination, and limited tailored resources *[279]*. Transgender women assigned male at birth have similar prostate cancer risks as cisgender men, but PSA testing guidelines are primarily designed for cisgender individuals *[279]*. Before starting gender-affirming hormone therapy, LGBTIQA+ individuals are advised to undergo PSA testing and MRI scans, as post-treatment MRIs can be difficult to interpret, and radiation is possibly less effective if the prostate has shrunk *[279]*. However, gender-affirming hormone therapy reduces testosterone levels, thereby likely lowering the overall risk of prostate cancer but also making traditional PSA level cutoffs redundant in this group.

Transgender women might encounter issues such as unrecognized trans status by health professionals, which can result to delayed early diagnosis and misinterpreted symptoms *[143]*. Additionally, PSA test results may be affected by hormone use, and symptoms could be confused for effects related to gender-affirming surgeries *[143]*.

A 2019 Australian-based online survey of transgender individuals' experiences with cancer care revealed that, 83.3% did not receive recommendations to screen for prostate cancer from their healthcare providers *[221]*. Of these, 37.5% were over 50 years, 37.5% were screened once, and 25% regularly screened. Overall, only 20.8% had been screened for prostate cancer. This survey further noted that trans women were frequently turned away by GPs, received inadequate tailored information, and lacked discussions about initiating testing.

The adverse effects of prostate cancer treatment have been reported to be more severe for LGBTIQA+ individuals. For instance, men who have sex with other men may not be able to perform their usual sexual roles post-treatment, leading to significant psychological distress *[252]*. Furthermore, the lack of tailored support and resources further exacerbates these issues, underscoring the need for more inclusive care. Published studies highlighted a need for more research and awareness among healthcare providers to better understand and address the disparities experienced by this expanding community *[279]*, *[143]*. Additionally, there is limited information on how care for prostate cancer differs between heterosexual and homosexual individuals, especially when both male partners are diagnosed *[347]*.

People with disability

The risks and outcomes of prostate cancer in Australian people with disabilities is unknown. Approximately 45% of Australian males aged in their 60s have a disability and about 10% of Australian males in this age have a profound or severe limitation *[110]*.

A US based study showed that men with disabilities were approximately 25% less likely than those without disability to participate in PSA testing, particularly in those who were deaf and blind *[234]*. A 2021 Korean-based study found that disabled people diagnosed with prostate cancer experience higher overall and prostate cancer-specific mortality rates *[311]*. Additionally, these individuals are more likely to receive androgen deprivation therapy rather than surgery and tend to undergo less comprehensive staging work-up. However, these studies under-represent individuals with permanent disabilities, which may lead to an underestimation of the true prostate cancer risk within this population. No direct evidence on PSA testing, patterns of care or mortality in the Australian disability community were found.

The National Disability Insurance Scheme (NDIS), launched in 2013, was designed to provide tailored support to individuals under 65 with significant or potentially permanent disabilities *[241]*. By 2021, around 450,000 people were receiving NDIS support, representing about one-third of those with severe disabilities. The scheme redirected funding and resources from National Disability Services and state-based programs that had previously supported a broader range of individuals with disabilities.

However, disabled cancer patients experience challenges in navigating the NDIS *[338]*. A qualitative study in NSW found that cancer patients and their families experience delays in receiving equipment, difficulties understanding the application process, and inconsistencies in both who they can contact for assistance, as well as in the outcomes of their plans.

Public and private healthcare services

Research has consistently shown that Australian individuals with private health insurance are more likely to participate in PSA testing *[255]*. Private health insurance is also associated with a higher likelihood of undergoing radical prostatectomy, while uninsured patients are more likely to receive external beam radiotherapy *[350]*. A 2012 cohort study revealed that prostate cancer patients without private insurance were more than twice as likely to experience treatment delays exceeding 70 days *[122]*. The study also found while the Australian public hospital system provides free medical treatment, leading many to have private insurance for faster access, economic status did not significantly affect the length of diagnostic or treatment intervals. Access to care varies between public and private systems and an individual's ability to access these systems.

Firefighters

There is an increased prostate cancer risk among firefighters in Australia *[187]*. An Australian study found that firefighters, both full-time (SIR=1.20) and part-time (SIR=1.40), had higher incidence rates of prostate cancer compared to the general population in 2010 *[186]*. The risk increased with for those employment for more than 10 years, suggesting a potential association between firefighting and elevated prostate cancer risk. Similarly, volunteer firefighters who have served for more than 10 years have 1.12 times higher risk of prostate cancer compared to the general population *[346]*.

Although firefighters are exposed to suspected carcinogens associated with prostate cancer, the biological pathway is unclear *[346]*. A potential explanation for higher incidence prostate cancer rates among firefighters is the mandatory routine health check-up, which may lead to more frequent diagnoses through higher testing. However, further research exploring the association between firefighters and clinically significant prostate cancer or prostate cancer death in the Australian context is needed.

Military veterans

In Australia, the Department of Veterans Affairs provides full funding for military veterans diagnosed with prostate cancer under its Non-Liability Health Care (NLHC) program *[161]*. NLHC covers a wide range of cancer treatments, including allied health services, GP and specialist care, scans, blood tests, as well as treatments such as chemotherapy, radiation therapy, surgery, and hormone therapy.

Studies have found an association between military veterans and an increased risk of prostate cancer *[320]*, *[334]*. Although there is limited research on prostate cancer rates among Australian Defense Force personnel, some studies have explored the risk among Australian veterans

from the Vietnam War *[299]*. The role of chemical exposure, particularly Agent Orange, which has potential carcinogenic effects is not well understood *[231]*.

Prisoners

Cancer diagnoses among prisons have increased significantly over time, with wait times for diagnosis reaching up to 30 weeks in 2024 *[289]*. A Victorian study conducted between 2002 and 2016 found that 4.5% of prisoners aged 45 to 55 were diagnosed with prostate cancer *[259]*. While there is a significant lack of data on the risks and impact of prostate cancer among prisoners in Australia, an international study provides brief understanding of prostate cancer care in prison.

A 2023 mixed study in Uganda examined the barriers and facilitators to prostate cancer testing among prisoners *[103]*. The study found that limited knowledge of prostate cancer and a lack of screening services in prisons hindered participation in screenings. Participants recommended raising awareness, conducting outreach screenings, providing appropriate screening equipment, and training prison health staff to improve participation and enhance screening capacity at prison health centres.

Overall, this population has been largely understudied, and more efforts are needed to understand the disparities and barriers this populations experiences in accessing prostate cancer care.

Summary

In the last decade, there have been improvements in the understanding of prostate cancer detection and outcomes in selected socio demographic groups. However, significant gaps in understanding regarding specific priority populations remain. These gaps include issues regarding potential drivers of inequity in outcomes, the factors influencing these outcomes, as well as potential solutions to address the known inequities. More research is needed to address the gaps and more information can be found in the Dissemination plan.

Aboriginal and Torres Strait Islander populations Advisory Group report

Health status of Aboriginal and Torres Strait Islander males

Before colonisation, Aboriginal and Torres Strait Islander males had active tribal roles with authority and status within their family, community and kinship systems *[97]*. Eldership of men was responsible for cultural obligations through maintaining ceremonies, sacred objects, songlines, and performing rituals. Through their leadership, they educated the young men, advising them on the kinship system and relationships, and they were custodians of the law. Through cultural initiation, they taught young men about their rights and obligations. Since colonisation, some parts of Australia have experienced a significant erosion of cultural practices and traditional ways *[94]*. This cultural undermining has led to many men losing their cultural identity and obligations to their country and kinship system *[94]*. While this sense of loss may not be visible, it has a direct impact on the health and well-being of Aboriginal and Torres Strait Islander males today.

The health status of Aboriginal and Torres Strait Islander males is significantly worse than that of non-Indigenous men on every health and socioeconomic indicator. Many factors contribute to the health gap between Aboriginal and Torres Strait Islander males and non-Indigenous, including lifestyle risk factors, physical environmental factors and health service access and utilisation. Aboriginal and Torres Strait Islanders experience a significantly higher cancer burden compared to non-Indigenous people, with lung, breast, bowel, and prostate cancers being the most common. Aboriginal and Torres Strait Islander males have a lower participation rate in health screening programs, including for prostate cancer, compared to non-Indigenous populations. These disparities persist even after adjusting for socioeconomic factors, remoteness, and cancer stage at diagnosis *[323]*, *[158]*.

Prostate cancer in Aboriginal and Torres Strait Islander males

Detailed epidemiological data on prostate cancer and PSA testing rates in Aboriginal and Torres Strait Islander males are limited. These data gaps are well-known and widely acknowledged, with accurate estimates traditionally hindered by the incomplete identification of Aboriginal and Torres Strait Islander status in Cancer Registration processes *[65]*, *[95]*, *[151]*, *[154]*.

According to the most recent national data (NSW, VIC, Qld, WA, NT) from the Australian Institute of Health and Welfare (AIHW), prostate cancer is the most common cancer diagnosed in Aboriginal and Torres Strait Islander males *[65]*. Between 2014 and 2018, the incidence rate of prostate cancer was 43 per 100,000 population, which is a lower rate (0.8) than for non-Indigenous males *[65]*. Prostate cancer accounted for 5.8% of cancer deaths of Aboriginal and Torres Strait Islander males in this period *[65]*.

When stratified by age, prostate cancer incidence rates in Aboriginal and Torres Strait Islander males are 0.5 per 100,000 for those under 45, increasing to 648 per 100,000 for those 75 and over. Rates are generally lower than in non-Indigenous males, except for the 75 and over age group *[65]*. Recent data from the Victorian Cancer Registry shows higher age-standardised incidence in Aboriginal and Torres Strait Islander males compared to non-Indigenous males *[21]*.

The national 5-year crude survival rate (2014-2018) was 77% for Aboriginal and Torres Strait Islander males, compared to 83% for non-Indigenous men *[65]*. Victorian estimates (2017-2021) report an 89% five-year relative survival rate in Aboriginal and Torres Strait Islander males versus 95% in non-Indigenous males *[21]*. Data also reveals a three-fold higher risk of death from prostate cancer in Aboriginal and Torres Strait Islander males in Victoria compared to non-Indigenous men. NSW Cancer Registry data (2016-2020) shows 576 new diagnoses and 88 deaths in NSW Aboriginal and Torres Strait Islander males *[22]*. This figure is significantly more than the figures reported above by the

AIHW and either indicates increased identification of Aboriginal and/or Torres Strait Islander status over time or systematic differences in reporting between the State and National data sets.

PSA testing in Aboriginal and Torres Strait Islander males

Previous prostate cancer guidelines recommended shared decision making for men aged 55-69 *[147]*. However, disparities exist in screening uptake between Aboriginal and Torres Strait Islander populations and non-Indigenous populations. Aboriginal and Torres Strait Islander people are less likely to participate in breast, cervical and bowel population screening programs than non-Aboriginal and Torres Strait Islanders. The National Bowel Cancer Screening Program, for example, has shown lower participation rates among Aboriginal and Torres Strait Islanders, highlighting the need for culturally sensitive approaches *[149]*.

As with epidemiological data, there are limitations to the data for calculating the screening participation rates for Aboriginal and Torres Strait Islander people due to under-reporting of Indigenous status *[65]*. PSA testing patterns in Australia show significant geographical and socioeconomic variations.[201, 203] Factors associated with higher PSA testing rates include frequent GP consultations, benign prostatic hyperplasia treatment, and age 60-69 years. PSA testing rates in Australia have decreased since 2007, with variations across regions and socioeconomic groups, including Aboriginal and Torres Strait Islander males *[227]*.

For prostate cancer, the 2018–19 National Aboriginal and Torres Strait Islander Health Survey (NATSIHS) showed that 58% (36,600) of Aboriginal and Torres Strait Islander males aged 50 and over reported having been tested for prostate cancer at least once *[67]*. Two older studies (low quality) also suggest that PSA testing is lower in Aboriginal and Torres Strait Islander males compared to non-Indigenous men (11.4% vs 34.1%) *[23]*, *[24]*.

Stage at diagnosis

For all cancers, after adjustment for age, sex, remoteness, Socio-Economic Indexes for Areas (SEIFA) and diagnostic year, Aboriginal and Torres Strait Islander people are more likely to be diagnosed with late stage disease compared with non-Aboriginal people (OR 1.59, 95%CI 1.45–1.75), including for prostate cancer specifically (OR 2.59, 95%CI 1.65–4.08). Further, diagnosis with distant stage (all cancers) in age-stratified analyses is more pronounced for Aboriginal and Torres Strait Islander people aged under 50 years (OR 1.51, 95%CI 1.20–1.91) *[324]*.

Prostate cancer patterns of care

A small study (n=87) reported prostate cancer patterns of care and morality outcomes in NSW in the period 2000-2011 *[25]*. It showed:

- Aboriginal and Torres Strait Islander males with prostate cancer were more likely to live outside major cities and more likely to live in socio-demographic disadvantaged areas than non-Indigenous men with prostate cancer;
- Mortality from prostate cancer in Aboriginal and Torres Strait Islander males was 49% higher than non-Indigenous men after adjusting for age, stage and comorbidities;
- There was no significant difference in age at diagnosis or spread of disease at diagnosis; and
- Aboriginal and Torres Strait Islander males were less likely to have a radical prostatectomy than non-Indigenous men (OR 0.60, 95% CI 0.40–0.91).

Cultural considerations related to prostate cancer

There are strong cultural practices which affect approaches to prostate cancer in Aboriginal and Torres Strait Islander communities *[95]*. For many Aboriginal and Torres Strait Islander males, prostate health and cancer are seen as men's business and associated with 'shame' and death, leading to a reluctance to engage with health services *[68]*. These matters are traditionally seen as taboo, requiring culturally appropriate and gender-specific health services *[69]*. Additionally, Aboriginal and Torres Strait Islander males have low levels of help-seeking behaviours compared with non-Indigenous men *[95]*, *[208]* with barriers to help-seeking including culturally inappropriate services, lack of awareness, lack of knowledge and shame *[24]*, *[68]*' *[344]*.

Aboriginal and Torres Strait Islander males report having difficulties talking to health professionals, with particular concerns around breach of confidentiality within the community and stigma associated with sexual problems *[151]*. A lack of culturally appropriate health services for men has been highlighted as a barrier for Aboriginal and Torres Strait Islander males with reproductive problems, particularly, the predominance of female health professionals and the lack of integration of cultural aspects of family and gender into men's health care *[70]*.

Health system barriers to care

Generally, Aboriginal and Torres Strait Islander people face significant challenges in accessing cancer treatment services, particularly for prostate cancer. They experience higher cancer mortality rates despite lower incidence, attributed to poor access to healthcare services, cultural disconnects with mainstream services, and elevated comorbidities *[287]*, *[257]*. While differences in treatment and comorbidities can explain some disparities, substantial unexplained gaps remain, highlighting the need for further research and targeted interventions to improve cancer outcomes for Aboriginal and Torres Strait Islander males *[158]*.

Several recent studies have also hypothesised about barriers in the health system that may contribute to poor outcomes in Aboriginal and Torres Strait Islander males with prostate cancer, these include:

- Aboriginal and Torres Strait Islander males have poor knowledge of prostate cancer *[95]*, *[25]*.

- Increasing use of technologies, e.g. MRI, to improve the diagnosis, monitoring and treatment of prostate cancer but may be less likely to benefit Aboriginal and Torres Strait Islander males in NSW because of equity issues *[25]*, *[308]*.

Recommendations

As data for prostate cancer and PSA testing in Aboriginal and Torres Strait Islander men is still evolving, based on extensive consumer consultation and contextual analysis, the Aboriginal and Torres Strait Islander Advisory Group make the following recommendations.

- PSA Testing for Aboriginal and Torres Strait Islander men should be embedded into the annual Aboriginal and Torres Strait Islander free annual health assessment program
- Through programs such as the Medical Specialist Outreach Assistance Program (MSOAP), existing telehealth infrastructure, and point of care testing for PSA in Aboriginal Community Controlled Health Organisations, Aboriginal and Torres Strait Islander men, particularly in rural and remote communities, have facilitated access to specialist diagnostic and treatment services once they are identified as at-risk. These existing infrastructures can be utilised to support men undergoing PSA testing who require further testing/care.
- **Research and Data Quality**: Further targeted research on prostate cancer in marginalised groups, such as Aboriginal and Torres Strait Islander populations, with a focus on improving data quality through better surveillance and monitoring.
- **Prevention and Health Promotion**: Develop and implement targeted, culturally appropriate health promotion/education campaigns for Aboriginal and Torres Strait Islander men to reduce stigma around screening and increase awareness of prostate cancer, that commence early and run in parallel with the free annual health assessment program.
- **Continued Research and Targeted Interventions**: Ongoing research and targeted interventions are essential to improve prostate cancer outcomes for Aboriginal and Torres Strait Islander men.

Rationale

The National Aboriginal and Torres Strait Islander Health Plan 2021-2031 *[69]* provides an overarching policy framework for Aboriginal and Torres Strait Islander health and wellbeing. 'Priority Five' focuses on accessible, early intervention approaches that provide timely, high quality, effective, culturally safe and responsive care. This includes a dedicated objective to deliver targeted action to improve cancer screening rates and care pathways for treatment, including addressing barriers to identifying, treating, and managing cancer.

Embedding of PSA testing into the existing annual Aboriginal and Torres Strait Islander free annual health assessment program will likely improve PSA testing rates as program uptake continues to grow. The Australian Government provides general practitioners (GPs) with health assessments and checks for Aboriginal and Torres Strait Islander people under the Medicare Benefits Schedule (MBS). The MBS Item 715 is a general health assessment for Aboriginal and Torres Strait Islander people. It is used for detecting a range of potential health issues that may need follow-up care such (e.g., hypertension, hyperglycaemia, oral health, mental health, sexual health, immunisation status, hearing and vision) *[73]*. Between 2009–10 and 2018–19, the access rate for the Aboriginal and Torres Strait Islander annual health assessments through the Medicare Benefits Schedule increased from 68 checks per 1,000 population to 297 per 1,000 population *[202]*.

The National Community Controlled Health Organisation (NACCHO) Male Health Blueprint 2013 – 2030 calls for the delivery of community-controlled, comprehensive primary male health care services that are culturally safe, culturally appropriate and accessible and assist Aboriginal and Torres Strait Islander men to rebuild their cultural and spiritual strengths, which define their identity *[74]*.

Cultural safety issues in the Australian health system significantly impact Aboriginal and Torres Strait Islander men's prostate cancer care *[95]*. Key challenges include communication barriers, lack of cultural understanding, and limited service access *[309]* *[298]*. Aboriginal and Torres Strait Islander men often face logistical difficulties, such as transportation and accommodation problems, particularly in rural areas *[309]*. To address these issues, health services should reorient their models of care to include specific roles of Aboriginal and Torres Strait Islander men and break down the cultural protocols of men's businesses *[322]*. Creating a culture of respect, providing culturally safe environments, and involving family and community support are crucial *[322]*, *[296]*. Additionally, recognising Aboriginal and Torres Strait Islander men's preferred approaches, such as pragmatism and humour, can improve engagement with cancer care *[258]*. Aboriginal and Torres Strait Islander health professionals play a vital role in providing culturally competent care and increasing the accessibility of cancer services *[160]*.

Appendix 4: Organisations to be approached for endorsement of the 2025 Guidelines

Key stakeholders approached in 2016

Organisation	Organisation type
Medical Oncology Group of Australia Incorporated (MOGA)	Professional organisation - Medical
Royal Australian and New Zealand College of Radiologists (RANZCR)	Professional organisation - Medical
Royal Australian College of General Practitioners (RACGP)	Professional organisation - Medical

Royal Australian College of Physicians – Australian Chapter of Palliative Medicine (AChPM, RACP)	Professional organisation - Medical
Royal Australian College of Physicians – Australian Faculty of Public Health Medicine (AFPHM, RACP)	Professional organisation - Medical
Royal Australian College of Physicians (RACP) – Adult Health Division	Professional organisation - Medical
Royal Australian College of Surgeons (RACS)	Professional organisation - Medical
Royal College of Pathologists of Australia (RCPA)	Professional organisation - Medical
The Royal Australian College of Remote and Rural Medicine (ACRRM)	Professional organisation - Medical
Urological Society of Australia and New Zealand (USANZ)	Professional organisation - Medical

Organisations represented in Review Group

Organisation	Organisation type
Indigenous Wellbeing Centre	Aboriginal and Torres Strait Islander men
Australian Catholic University	Academic
Bond University	Academic
Edith Cowan University	Academic
Garvin Institute for Medical Research	Academic
Griffith University	Academic
James Cook University	Academic
Monash University	Academic
University of Queensland	Academic
University of Southern Queensland	Academic
University of Sydney	Academic
University of Western Australia	Academic
AndroUrology	Healthcare provider
Australian Urology Associates	Healthcare provider
Deepdene Surgery	Healthcare provider
Emerald Medical Group	Healthcare provider
Icon Cancer Centre	Healthcare provider
MQ Health	Healthcare provider
Peter MacCallum Cancer Centre	Healthcare provider
The Urological Cancer Centre	Healthcare provider
DoD HEROIC Prostate Cancer Precision Health Africa1K	Men of African descent
OCI Foundation	Men of African descent
Douglass Hanly Moir Pathology	Pathology
Melbourne Pathology	Pathology
QML Laboratory	Pathology
St Vincent's Pathology	Pathology

Organisation	Organisation type
Cancer Council QLD	Professional organisation - Health
Daffodil Centre	Professional organisation - Health
QLD Xray	Professional organisation - Medical
SA Prostate Cancer Clinical Outcomes Collaborative	Professional organisation - Medical

Additional organisations

Organisation	Organisation type
Australian Indigenous HealthInfoNet	Aboriginal and Torres Strait Islander men
Australian Institute of Aboriginal and Torres Strait Islander Studies (AIATSIS)	Aboriginal and Torres Strait Islander men
National Aboriginal Community Controlled Health Organisation (NACCHO)	Aboriginal and Torres Strait Islander men
National Indigenous Australians Agency	Aboriginal and Torres Strait Islander men
Culturally and Linguistically Diverse Communities Health Advisory Group	CALD
Federation of Ethnic Communities' Councils of Australia	CALD
Australian Multicultural Health Collaborative	CALD
Men's Health Melbourne	Consumer
Men's Health Australia	Consumer
Australian Men's Health Forum	Consumer
Australian Federation of Disability Organisations	Disability
Cancer Institute of NSW	Government
NSW Department of Health	Government
ACT Department of Health	Government
VIC Department of Health	Government
WA Department of Health	Government
TAS Department of Health	Government
SA Department of Health	Government
NT Department of Health	Government
QLD Department of Health	Government
Cancer Australia	Government
Department of Veterans' Affairs	Industrial exposure
Veteran Health Association	Industrial exposure
Australasian Fire and Emergency Service Authorities Council/Australian Fire Authorities Council	Industrial exposure
Diversity Council Australia	LGBTIQA+
LGBTIQ+ Health Australia	LGBTIQA+
Pride Foundation Australia	LGBTIQA+
Australian Professional Association for Trans Health	LGBTIQA+
ACON	LGBTIQA+

Organisation	Organisation type
Transgender Victoria	LGBTIQA+
Rainbow Health Australia	LGBTIQA+
African Communities Foundation Australia	Men of African descent
African Australian Advocacy Centre	Men of African descent
African Australian Network Alliance Ltd	Men of African descent
Cancer Council Australia	Professional organisation - Cancer
Cancer Council ACT	Professional organisation - Cancer
Cancer Council NSW	Professional organisation - Cancer
Cancer Council VIC	Professional organisation - Cancer
Cancer Council NT	Professional organisation - Cancer
Cancer Council SA	Professional organisation - Cancer
Cancer Council WA	Professional organisation - Cancer
Cancer Council TAS	Professional organisation - Cancer
Australian Health Promotion Association	Professional organisation - Health
Public Health Association of Australia	Professional organisation - Health
Clinical Oncology Society of Australia (COSA)	Professional organisation – Clinical
The Australian Medical Association (AMA)	Professional organisation – Clinical
Australia New Zealand Urological Nurses Society (ANZUNS)	Professional organisation – Clinical
Australian Nursing and Midwifery Federation	Professional organisation – Clinical
Australian College of Nurse Practitioners	Professional organisation – Clinical
Australian College of Nursing	Professional organisation – Clinical
Australian Primary Health Care Nurses Association (APNA)	Professional organisation – Clinical
Cancer Nurses Society of Australia	Professional organisation – Clinical
Continence Nurses Society Australia	Professional organisation - Clinical

Appendix 5: Glossary of terms

Term	Definition
Active surveillance	The definition of active surveillance is a monitoring strategy for patients with clinically localised prostate cancer.
Androgen	A broad term for any natural or synthetic compound, usually a steroid hormone (e.g. testosterone), that stimulates or controls the development and maintenance of male characteristics.
Androgen deprivation therapy (ADT)	A form of prostate cancer treatment where drugs are used to reduce the levels of male hormones or blocking the effect of androgens on the growth of cancerous cells in the prostate.
Asymptomatic	Not having symptoms, symptom-free.
Average risk	A man's expected risk of developing prostate cancer estimated from the rate of occurrence of prostate cancer in all men in that population. For practical purposes and in these Guidelines, men are usually assumed to be not at higher risk of prostate cancer unless they

Term	Definition
	have one or more risk factors for prostate cancer that clearly distinguish their level of risk from that of most other men in the population
Benefits (of a test or treatment)	The range of desirable effects that have been observed at the population level. In this document, 'benefits and potential harms' indicate potential outcomes, which will not necessarily occur in the case of an individual man.
Biopsy of the prostate	Removal of small pieces of tissue from the prostate, usually using a needle. Tissue samples are taken from different areas of the prostate, and then examined under the microscope to see if they are cancerous.
Biopsy naïve	Individuals who have not previously undergone a prostate biopsy.
Biparametric MRI	The combination of two different MRI techniques to image tissue in the human body.
Chemotherapy	The treatment of cancer using specific systemic chemical agents or drugs that are destructive to malignant cells and tissues.
Clinically insignificant prostate cancer	Prostate cancer that is ISUP grade group 2 or less. These cancers are less likely to grow and spread.
Clinically significant prostate cancer	Prostate cancer that is ISUP grade group 2 or more. These cancers are at increased risk of growing and spreading.
Consensus-based recommendation	A recommendation based on clinical expertise, expert opinion and available evidence, and formulated using a consensus process, after a systematic review of the evidence found insufficient evidence on which to base a recommendation
Confidence interval (CI)	A measure that quantifies the uncertainty in measurement. When reported as 95% CI, it is the range of values within which we can be 95% sure that the true value for the whole population lies.
Decision aids	A decision aid is an intervention that provides information on clinical options and outcomes relevant to a patient's health. It is designed to help people make specific choices about different options for their healthcare by providing information on the relevant clinical options and outcomes.
Definitive treatment	Treatment intended to cure a condition.
Depression	A general and long-lasting feeling of being down, often associated with tearfulness, guilt or irritability. Other features include loss of interest or pleasure in activities, lowered energy levels, poor concentration and troubles with sleep and appetite.
Digital rectal examination (DRE)	An examination of the prostate through the wall of the rectum. The doctor inserts a finger in the rectum and feels the shape of the prostate. Irregularities may be caused by cancer
Evidence	Data on the effectiveness of a treatment or intervention derived from studies that compare it with an appropriate alternative. Preferably the evidence is derived from a good-quality randomised controlled trial, but it may not be. In areas of medicine that do not involve a therapeutic intervention, such as diagnosis, prognosis, aetiology and screening, evidence constitutes knowledge derived from properly conducted clinical or health services research
Evidence-based guideline	A recommendation based on the best available evidence identified by a systematic review of evidence
Evidence-based recommendation	A recommendation formulated after a systematic review of the evidence, indicating supporting references.
Gleason score	A way of grading cancer cells. Low-grade cancers (Gleason score 2, 3, 4) are slower growing than high-grade (Gleason scores 8, 9, 10) cancers. The pathologist identifies the two most common tissue patterns and grades them from 1 (least aggressive) to 5 (most aggressive). The Gleason score is given as two numbers added together to give a score out of 10 (for example, 3 + 4 = 7). The first number is the most common pattern seen under the microscope and the second number is the next most common. Refer Gleason Score and ISUP Grade

Term	Definition
Grade	A way of describing how abnormal the cancer cells look, and consequently how aggressive or fast-growing the cancer is likely to be. The most commonly used grading system is the Gleason score, which ranges from 2 to 10 (see Gleason score).
Good Practice Statement	A point of guidance to support the evidence-based recommendations, based on expert opinion and formulated by a consensus process, on a subject outside the scope of the systematic reviews.
2016 Guidelines	2016 Clinical Practice Guidelines for Prostate Specific Antigen (PSA) Testing and Early Management of Test-detected Prostate Cancer
Harms (of a test or treatment)	The range of unwanted effects that have been observed at the population level. In this document, 'benefits and potential harms' indicates potential outcomes, which will not necessarily occur in the case of an individual man.
Hazard ratio (HR)	A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any particular moment in a group of patients who have been given a specific treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.
High risk	For the purposes of this review, males are considered to be at higher risk if they have a risk of clinically significant prostate cancer or prostate cancer death that is at least double that of the overall risk for the Australian male population. Refer Section A: Risk Assessment.
Incidence	The number of new cases of a disease or condition among a certain group of people within a certain period of time.
Intervention	An action that produces an effect or that is intended to alter the course of a process.
Life expectancy	The probable number of years a person will live after a given age, as determined by mortality in a specific geographic area. It may be individually qualified by the person's condition or race, sex, age, or other demographic or clinical factors
Magnetic resonance imaging (MRI)	A way of imaging the inside of the body using magnetic forces and without using x-rays.
Metastasis	The secondary or distant spread of cancer, away from its primary (initial) site in the body.
Metastatic	Relating to secondary cancer.
Minimal clinically important differences (MCID)	Refer Minimal clinically important differences.
Monitoring	The process in which patients are followed up after initial diagnosis and treatment. Monitoring may include clinical examination and/or the regular performance of tests.
Morbidity	The rate of incidence of a disease or the proportion of a disease in a geographic location or community.
Mortality	The relative frequency of deaths in a specific population.
Multiparametric MRI (mpMRI)	The combination of two or more different MRI techniques to image tissue in the human body. Refer 6. Specialist setting - Multiparametric magnetic resonance imaging.
Oncologist	A specialist in the treatment of cancer.
Priority populations	Priority populations are specific Australian population groups that often experience poorer health outcomes and may face barriers to accessing healthcare. Targeted and tailored health interventions and resources are necessary for priority populations to deliver equitable healthcare to all Australians. Considerations for priority populations in the context of prostate cancer are detailed in Section C: Priority populations.
Prognosis	The course and likely outcome of a disease, as estimated by a person's doctor or treatment team.
Prostatectomy	An operation to remove all or part of the prostate.

Term	Definition
Protocol	A well-defined program for treatment
Prostate-specific antigen (PSA)	A protein produced by the cells in the prostate, which is usually found in the blood in larger amounts when prostate cancer is present. It can exist in the blood in free form (free PSA), or bound with other substances (also called bound or complexed PSA). PSA may be used as a test for prostate cancer or to monitor its recurrence.
Prostatectomy (radical prostatectomy)	An operation which removes the prostate and the seminal vesicles. This is usually done through a cut in the lower abdomen.
PSA velocity	Defined as an absolute annual increase in serum PSA, and is expressed as µg/L /year. Calculating PSA velocity requires several PSA measurements separated by several months
Quality of life (QOL)	A person's overall appraisal of his or her situation and wellbeing.
Radiation oncologist	A specialist in the treatment of cancer using x-ray techniques.
Radiotherapy	The use of radiation, such as x-rays, gamma rays, electron beams or protons, to kill or damage cancer cells and stop them from growing and multiplying. It is a localised treatment, which means it generally only affects the part of the body where the radiation is directed.
Randomised controlled trial	A prospective study that measures the effectiveness of a new intervention or treatment. Randomisation reduces bias and provides a rigorous tool to examine cause-effect relationships between an intervention and outcome.
Relative risk	A measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group.
Reliability (of a test)	The ability to measure something in a reproducible and consistent fashion.
Response	A change in the size or extent of disease due to treatment.
Saturation biopsy	A technique in which multiple biopsies are dispersed in a systematic manner throughout the entire prostate gland, thereby 'saturating' the gland with sampling
Sensitivity	The conditional probability that a person having a disease will be correctly identified by a clinical test. This is expressed as the number of true positive results divided by the total number with the disease (which is the sum of the numbers of true positive plus false negative results).
Specificity	The statistical probability that an individual who does not have the particular disease being tested for will be correctly identified as negative, expressed as the proportion of true negative results to the total of true negative and false positive results.
Staging	The process of determining the extent of the disease. A system for describing how far the cancer has spread. Refer TNM staging prostate cancer.
Support	People on whom the patient can rely for emotional caring, and reinforcement of a sense of personal worth and value. Other components of support may include practical help, guidance, feedback and someone to talk to.
Symptoms of prostate cancer	The most common and noticeable symptoms of prostate cancer are changes and problems with urinating, including: • The urge to urinate more than usual during the day and night (noting that waking once a night can be normal for men as they get older); • Sudden or urgent need to urinate, which is difficult to stop; • Problems urinating such as: ◦ Straining or trouble starting a stream ◦ Not being able to urinate when the feeling is there ◦ Poor urine flow, which may stop and start ◦ Dribbling at the beginning or end of urinating ◦ Discomfort or pain when urinating ◦ Feeling unable to fully empty the bladder.
Systematic review	A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise the relevant literature, and to collect and analyse data

Term	Definition
	from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Total PSA	The sum of the free and bound forms of the protein measured in a blood sample, which is measured with a standard PSA test.
Trans-rectal ultrasound (TRUS)	A means of imaging the prostate in order to locate cancer. The ultrasound probe is placed in the rectum.
Tumour	Any swelling. In the context of cancer, the word usually refers to malignant (cancerous) lumps.
Urethra	The tube which carries urine and ejaculate along the length of the penis and to the outside.
Urologist	A physician who has specialised knowledge and skill regarding problems of the male and female urinary tract and the male reproductive organs.
Watchful waiting	A conservative strategy for managing prostate cancer. Refer 9. Watchful waiting..

Supplementary explanations and definitions

Gleason Score and ISUP Grade

Gleason Score and ISUP grade are ways of determining how likely it is that a prostate cancer will grow and spread. They are both derived from the Gleason grade.

Gleason grade

Gleason grade is determined by a pathologist after examining prostate biopsy samples under a microscope. Normal prostate cell grows in an orderly and predictable pattern but as they become cancerous their growth pattern becomes disorderly and erratic. These patterns are numbered Gleason grade 1 to 5 with 1 being normal prostate cells and 5 being aggressive cancerous cells.

Gleason score

It is common for more than one type of Gleason grade pattern to be present in a prostate biopsy sample. By identifying the most common and second most pattern, the pathologist will determine a Gleason score for the cancer. For example, if the first and second most common Gleason grade patterns in your prostate biopsy are scored 3, then your Gleason score will be 3 + 3 = 6. If the first most common pattern is 3 and the second most common pattern is 4 your Gleason score will be 3 + 4 = 7. The higher your score, the higher your cancer grade and the higher the risk of your cancer growing and spreading quickly.

ISUP Grade

The ISUP (International Society of Urological Pathology) grade group is an internationally recognised way of predicting how quickly a prostate cancer is likely to spread. It uses a 1 to 5 grade group system where the higher the number, the greater the risk that a cancer will be aggressive and spread rapidly. In developing these Guidelines for the early detection of prostate cancer, ISUP ≥ 2 is considered to be clinically significant cancer. The table below shows the Gleason Score and the corresponding ISUP grade group.

Gleason Score and ISUP Grade

ISUP Grade Group	Gleason Score	Prostate cancer risk
1	3 + 3 = 6	Low risk: the cancer is usually slow growing and less likely to spread
2	3 + 4 = 7	Intermediate favourable risk: the cancer can be moderately likely to spread
3	4 + 3 = 7	Intermediate unfavourable risk: the cancer can be moderately likely to spread
4	4 + 4 =8 3 + 5 = 8 5 + 3 = 8	High risk: the cancer can be fast growing and more likely to spread
5	4 + 5 = 9 5 + 4 = 9 5 + 5 =10	The highest risk: the cancer can be fast growing and most likely to spread

TNM staging prostate cancer

The TMN system is the standard international system for determining your cancer stage. It is made up of three parts:

- **T** - tumour stage. This is a score of T1 to T5 which corresponds to the size of the prostate cancer and how much of it has spread outside of the prostate. The lower the number (T1 to T2) the less the cancer has spread. The higher the number (T3 to T4) the more the cancer has spread.
- **N** - node stage. This refers to whether the cancer has spread into the lymph nodes in the pelvis. near to the prostate in your pelvis. It is a two-part score with N0 indicating that the cancer has not spread to the nearby lymph nodes and N1 indicating that it has.
- **M** - metastasis stage. This refers to whether the cancer has spread outside of the pelvis or to other parts of the body, such as bones or other organs. It is a two-part score with M0 indicating that there is no spread of cancer to other parts of the body and M1 indicating that the cancer has spread.

PI-RADS score

The Prostate Imaging Reporting and Data System (PI-RADS) is a standardised international reporting system for interpreting mpMRI images to determine if clinically significant prostate cancer is likely to be present.

Radiologists use PI-RADS to assign a score from 1 to 5 to suspicious areas (lesions) of the prostate based on how likely the lesion is to contain clinically significant ISUP ≥ 2 prostate cancer *[282]*, *[343]*, *[319]*.

PI-RADS scoring

PI-RADS score	Likelihood that clinically significant prostate cancer is present
PI-RADS 1	Very low
PI-RADS 2	Low
PI-RADS 3	Intermediate (undetermined)
PI-RADS 4	High
PI-RADS 5	Very high

PI-RADS was developed through an international collaboration involving the American College of Radiology (ACR), the European Society of Uroradiology (ESUR), and the AdMeTech Foundation. More information can be found by following this link ACR Prostate Imaging Reporting & Data System (PI-RADS).

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 systematic review data and to determine the clinical significance of an observed effect. They 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 *[313]*, *[332]*, *[247]* and advice from experts.

There are no published MCIDs for dichotomous prostate cancer outcomes. MCIDs for these outcomes were developed following GRADE guidance *[302]* by the MCID Working Group with support from the MRI, DRE and biopsy working groups. The MCID working group included a consumer, a general practitioner, a urology nurse practitioner and clinical specialists. More information on working groups can be found in Administrative report.

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, MRI, biopsy and DRE working groups taking into account any recent reports of patients' preferences. 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.

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	> 100/1000
4	MRI	G	Not required for these Guidelines
5	Biopsy	U	100/1000

5	Undetected ISUP grade 1 with close follow-up for those who are not biopsied	M	100/1000
6	Post biopsy infection	U	Not required for these Guidelines
7	Hospitalisation within 30 days of biopsy	M	50/1000
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	50/1000
9	Undetected ISUP grade ≥ grade 3 with close follow-up for those who are not biopsied	M	35/1000
10	Metastatic/advanced disease/ palliative therapy at 15 years follow-up	U, M	30/1000 – patients with localised prostate cancer 30/10000 screening populations
11	End of life	U	Not required for these Guidelines
12	Death at 15 years follow-up	U, M	15/1000 – patients with localised prostate cancer 15/10000 screening populations

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 [54] which reports patients' preferences with respect to MRIs and biopsies

Resources and useful links

Quick reference to international guidelines

Links to relevant guidelines.

American Urological Associate

Early Detection of Prostate Cancer: AUA/SUO Guideline (2023) - American Urological Association

American Cancer Society

American Cancer Society Recommendations for Prostate Cancer Early Detection | American Cancer Society

European guidelines

EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer 2025

Prostate Cancer Foundation (USA)

Prostate Cancer Foundation Screening Guidelines for Black Men in the United States

Prostate Cancer Foundation Highlights Evidence-Based Prostate Cancer Screening Guidelines for Black Men | Prostate Cancer Foundation

Royal Australia College of General Practitioners Australia

RACGP - Prostate cancer

The Lancet commission on prostate cancer (International)

The Lancet Commission on prostate cancer: planning for the surge in cases

Prostate Cancer Foundation of Australia

PCFA PSA-Testing-Guidelines.pdf

The National Comprehensive Cancer Network (NCCN, USA)

Prostate Cancer - Guidelines Detail

National Institute of Health and Care (NICE, UK)

Overview | Prostate cancer: diagnosis and management | Guidance | NICE

Resources for prostate cancer in sexually and gender diverse people

Resources to support clinicians to provide care tailored to people of diverse sexualities and genders are provided below:

- Cancer Council: LGBTQI+ People and Cancer: A guide for people with cancer, their families and friends
- NSW LGBTIQ+ Health Strategy 2022-2027
- LGBTIQA+ glossary of common terms
- The Rainbow Tick guide to LGBTI-inclusive practice, 2nd edition
- LGBTIQ+ training modules for medical professionals
- National Action Plan for the Health and Wellbeing of LGBTIQA+ People 2025–2035

Further resources specific to prostate cancer in gender diverse people are also available:

- Webinar: Considerations for transgender and gender diverse patients with prostate cancer
- Sexual and gender minorities with prostate cancer
- Prostate cancer in gay and bisexual men information booklets: diagnosis, treatment, side effects, wellbeing.
- Understanding Prostate cancer for LGBTIQA+ people
- Trans women and prostate cancer
- Prostate cancer in transgender women: what does a urologist need to know?

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