Response to NHMRC Draft Guideline Review

- Part 1: Response - Guidelines for the Early Detection of Prostate Cancer in Australia
- Part 2: Response to European Reviewer

Part 1: Response - Guidelines for the Early Detection of Prostate Cancer in Australia

We thank the reviewers for their feedback. All comments have been addressed as noted below.

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	Reviewer Comment	**NHMRC Comment**	**Developer Response**
1.	**Requirement A1 – suggestion** An explicit statement should be made that makes it clear that the Prostate Cancer Foundation of Australia was responsible for developing this guideline. While this is inferred from the wording of the preamble, an explicit statement to this effect would remove any ambiguity. I note that this has been included throughout the guideline and supporting documents but would suggest its inclusion in the preamble.	Please consider adding a clear statement that the Prostate Cancer Foundation of Australia was responsible for developing these guidelines.	The following heading and statement has now been added before the Dedication: **Guideline development** The Prostate Cancer Foundation of Australia was responsible for developing these Guidelines.
2.	**Requirement A6 – further information required** The developers of the guideline have presented a sensible strategy to document and manage the potential competing interests identified. This was informed by the NHMRC guidelines for guidelines. However, it appears that the conflicts of interest for all involved in the guideline development effort and their appropriate management strategies are not presented. The developers have stated that "Throughout the development process no significant conflicts of interest were identified, hence conflict management strategies were not considered necessary" (page 8 – document #4). Yet there are some conflicts of interest and management strategies listed in Table 1 – document #4. It is unclear if this table (review group conflict of interest declarations and management) refers to all groups included in the guideline, as it is labelled 'Review Group conflict of interest.' Although the governance structure and membership are listed in an appendix in document #1, there is no single group called 'Review Group.' We would suggest that a table similar to table 1 appears in the administrative report for all listed in the guideline effort per group, matching the list in the appendix of document #1.	Please create a revised table that includes conflict of interest declarations and management strategies for each individual involved in the guideline development (including those with no declared conflicts), grouped according to the governance structure. This consolidated table should be included in the administrative report to improve transparency and traceability.	A revised table has been added to the Administration Report submitted for NHMRC approval, now grouped according to the governance structure. Where Committee/Panel/Working Group members recused themselves from discussions pertaining to feedback provided by their organisation or collaborative group, this has now been explicitly noted in Table 1. For clarity, Section 2 – Declaring conflicts of interest, page 9 paragraph 3, has been revised to read: A convenor was nominated for each Committee/Panel/Working Group who did not have financial interests related to early detection of prostate cancer. Nominated

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			convenors were also free of non-financial interests. **Prior to the start of the Guideline review, a decision was made that,** in instances where group discussion was related to a convenor's conflict of interest, the convenor would nominate an Acting convenor for that period of discussion, and would not participate in Working Group activities related to the topic; including discussion, development of recommendations, and revision of recommendations. **However, based on assessment of ongoing declarations of interest until Guideline submission for approval, no conflicts of interest warranting these management strategies were identified.**
3.	**Requirement A8 – further information required** The guideline was developed with specific input from representative groups "The Guideline Review Group included: i) representatives for Aboriginal and Torres Strait Islander populations and Men of African Descent on the Expert Advisory Panel, and dedicated Expert Advisory Panel Working Groups for Aboriginal and Torres Strait Islander populations and Men of African Descent" (page 7 – document #4). However, the reason this criterion was scored as 'not met' is due to the process employed to recruit, involve and support these participants not being described in the section as indicated by the developers. It is suggested that this information be included with the above.	Please include a description of how representatives for Aboriginal and Torres Strait Islander populations and Men of African Descent were recruited, involved, and supported during the guideline development process in the administrative report.	The following has now been added to the Administration Report, Section 1.3 Representation of Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities (page 6): Representatives from culturally and linguistically diverse backgrounds were identified through recommendations by Steering Committee, Expert Advisory Panel and Working Groups, and directly contacted to provide information about the review and an opportunity to ask questions about involvement - refer Appendix 1: Review Group Invitations. During the Guideline development process, Working Group convenors supported representatives from culturally and

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			linguistically diverse backgrounds by contacting them out of session to allow private discussion as necessary. The final dot point on page 6 has been updated to include details of targeted consultation with peak bodies and organisations who represent Aboriginal and Torres Strait Islander peoples, LGBTQIA+ communities, and culturally and linguistically diverse communities undertaken in Public Consultation 2.
4.	**Requirement B1 – further information required** While The purpose of the guideline is clearly articulated, and while we acknowledge that the clinical questions are presented throughout sections A-E where appropriate and are clearly articulated in Appendix 2 of the guideline, they are not presented with the purpose of the guideline as requested. This is why this criterion has been scored as not met.	Please consolidate and list the clinical questions in the guideline (or technical report).	A consolidated question list has been added to the Technical Report under 'Purpose of the Guidelines'.
5.	**Requirement C3.2 *(Desirable)* – suggestion** We suggest that these considerations be included in any updates to this guideline, as this information can inform the evidence to decision tables.	If information is available, please add in the technical report search terms used to identify evidence related to consumers' perceptions and experiences.	Search strategies were not developed to systematically identify evidence of consumers' perceptions and experience as these issues are out of scope of the systematic reviews undertaken for the current Guideline. Considerations and evidence of consumers' perceptions and experience in the evidence to decision process was informed by clinical and epidemiological expertise in this area and consumer input. Systematic reviews addressing these issues will be considered for future Guideline updates
6.	**Requirement C3.4 *(Desirable)* – suggestion**	If information is available, please add in the technical report search terms used to identify evidence related to	Factors related to cost effectiveness and resource implications of practice are out of

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	We suggest that these considerations be included in any updates to this guideline, as this information can inform the evidence to decision tables.	cost effectiveness and resource implications of practice.	scope of the current review, but will be considered in future Guideline updates. Please note that a full economic evaluation of the Guidelines is an implementation priority (refer Dissemination Plan – Implementation Priority IP.8 Economic considerations) following Guideline approval.
7.	**Requirement D1 – action required** The wording of the recommendations is specific, unambiguous and clearly describes the actions that need to be taken (noting that the users in who the action needs to be taken are not specified, however given the target audience is clearly identified in the preamble of the guideline [health professionals in primary care and specialist urological settings], this omission is suitable). However, this criterion is scored as not met, as the wording of these recommendations do not always match the recommended wording as suggested by GRADE for the strength of the body of evidence. For example, the terminology "we recommend" is often used by GRADE members to signal a strong recommendation. The use of 'we suggest' signals the conditional nature of the recommendation. It is recommended that the strong and conditional recommendations be slightly re-worded to include this nuance.	Please reword the strong and conditional recommendations to align with GRADE guidance by using "we recommend" for strong recommendations and "we suggest" for conditional ones.	Strong and conditional recommendations have been reworded as to align with GRADE guidance as follows: • Strong recommendations - We recommend… • Conditional recommendations - We suggest… Additionally: • Consensus recommendations - We propose…
8.	**Requirement D7 – suggestion** We suggest that a statement to the effect that all recommendations were reached with full consensus is included in the final guideline where appropriate.	If no areas of major debate about the evidence and the recommendations were identified, please consider adding a statement that all recommendations were reached with full consensus.	A statement regarding consensus has now been added as the last sentence under Rationale where applicable in Sections A-E.

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9.	**Requirement D9.2 *(Desirable)* – suggestion** It is stated the GRADE evidence to decision framework (EtD) has been followed to inform recommendations. Although there are different criteria that can be considered as part of this framework depending on the perspective of the guideline and the type of recommendations being made (i.e. individual clinician/individual patient, individual clinician/population, coverage decision etc), resource use is standard in all versions and is mentioned in NHMRC Standard 6. We understand a cost-effectiveness study is out of scope, and that cost-effectiveness may be out of scope as a criterion in the EtD, however it would have been ideal if costs/ resources were considered. This would also be helpful to consider out of pocket costs (if any), as this is highlighted as a potential heading in the consumer companion to the guidelines.	Please consider including a brief explanation of whether and how resource use, including potential out-of-pocket costs, was considered in the evidence-to-decision process.	Resource use, including potential out-of-pocket costs, in the evidence-to-decision process is out of scope of the current review. Please note that a full economic evaluation of the Guidelines, including the above factors, is an implementation priority (refer Dissemination Plan – Implementation Priority IP.8 Economic considerations) following Guideline approval.
10.	**Requirement E8 – further information required** Appropriate Vancouver referencing has been used throughout the guideline. Several electronic references have been used, and the source location has been provided however the dates these websites have been accessed are not always stated for each reference. Some references have a date provided, but others do not. However, we acknowledge that this may be a difficult thing to address at this late stage.	Please consider adding the access date to all electronic references.	Where possible, access dates have been added to electronic references.
11.	**General – action required** Page xiii of document #1 – spelling error (form written instead of from).	Please correct spelling error.	This has been corrected.

Part 2: Response to European Reviewer received May 21, 2025

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The chosen evidence-based approach based on comprehensive literature with the GRADE methodology is commendable. It was not fully clear to me, however, whether systematic literature searches were conducted, as the reference list did not cover all the pertinent literature. Further, it seems that no meta-analyses were performed. I largely agree with the resulting recommendations, but do not fully concur on some issues. The following comments highlight the debatable aspects of the recommendation, and I hope focusing on them will not detract from the very positive overall impression I had of the recommendations.	We acknowledge the reviewer's positive comments, with thanks. Systematic literature searches were performed for each of the defined clinical questions and PICOs, and selection of studies for inclusion was in accordance with rigorous eligibility criteria developed by the technical team and expert working groups as described in the methods section of each systematic review report (see Technical Report). Further details of the search strategy and databases searched are found in the Appendices of each systematic review report in the Technical Report. Meta-analyses were planned where appropriate, where there were two or more studies reporting the same outcome, and if relevant, at corresponding time points. Meta-analyses was undertaken for DRE, mpMRI and Biopsy topics and results are documented in the technical reports and incorporated in the Summary of Findings tables.
Ideally cancer screening should be population-based with clearly defined protocol and governance by an authorized governmental organization. This allows comprehensive population coverage with harmonized protocol and standardized procedures. These features provide a higher population-level effectiveness than provision of screening in the context of health care attendance for other reasons (opportunistic screening).	These Guidelines represent a first step towards a planned testing program rather than a recommendation for an immediate transition to a population-based screening program. On this basis, we have reviewed the language used in the Guidelines, replacing references to an 'organised testing program' with a transition to a 'planned testing program. To further support this future transition, a research priority (following Guideline approval) is the monitoring of international and national research into organised testing pilot programs to determine effectiveness, appropriateness and requirements of a population-based screening program for the early detection of prostate cancer in Australia (RP.1 Organised testing program).
I would also like to highlight the difficulties inherent to shared decision making for screening. First, the evidence is complex and not easy to interpret, which can pose major issues for GPs. Second, communicating the key issues in a concrete	We share your sentiments on the difficulties inherent to shared decision making for screening. Development of decision support materials for a wide range of stakeholders are key implementation priorities (IP.4 Consumer companion and

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and understandable manner is challenging. Third, the evidence of improved level of understanding and decreased decisional regret is weak. Major effort in developing material for this aspect with contributions of substance experts, communication experts and lay stakeholders is crucial.	resources and IP.5 Support for primary care, specialists, and other health professionals), with a corresponding Research Priority (RP.5 Decision support) to understand: the preferences of consumers and clinicians regarding the nature, form and content of decision support tools; best practice for providing decision support for people considering prostate cancer testing; and the nature and content of effective clinical education about decision support.
Perhaps the most important issue that in my view merits further consideration is the target age range. The current evidence is based primarily on PSA screening and the trials do not show benefit from screening men older than 70 years. Indirect evidence can be inferred based on life expectancy, but such evidence should be downgraded due to indirectness. The German PROPBASE trial has shown exceedingly low risk of high-grade prostate cancer at age 45 years, which raises doubts about effectiveness and cost-effectiveness of screening at ages <50 years	No randomised controlled trials were found that compared PSA testing protocols with usual care for men aged 70 and over who had previously undergone regular PSA testing. The Working Group considered there was a need for consensus-based recommendations for these men as the risk of prostate cancer mortality rises with age and the life expectancy of Australian men aged 70 years is 16 years. PSA levels also rise with age and these consensus-based recommendations were based on considerations of Australian age-related PSA reference intervals. 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 found that compared PSA testing protocols with usual care for men aged 40-49 years. 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.
Another major point is whether both targeted and systematic biopsies should be used after MRI. The question is clearly value-based. It requires balancing the advantage of detecting more GG 2-5 cases against the disadvantage of increasing the detection of GG 1 cases, which are more likely to present harm than benefit. With targeted biopsies, a proportion of GG2 cases are also likely to represent low-gar, low-risk cases with minimal if any benefit from active therapeutic	We agree with the reviewer that patient values and preferences are an important consideration here, and came to consensus that most men indicated for an MRI-targeted biopsy would prefer to be diagnosed once and for all using a combined biopsy approach, rather than undergoing an initial MRI-targeted biopsy only, and a secondary systematic or combined biopsy procedure later. In the evidence tables for these clinical questions, we outline that we found strong evidence for

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intervention. This issue likely highlights the screening perspective emphasizing specificity (minimizing false positive findings) versus clinical viewpoint of active patient management. In the screening context, an important feature is the repeated nature of the process. Missing an early case at a screening round may still mean that a slowly growing tumor can still be curatively managed if detected at a subsequent screen. For this issue, evidence should be regarded as weak and the justification for the decision clearly described as value driven.	the harms i.e., ISUP grade ≥2 undetected, associated with not undertaking a systematic biopsy in addition to an MRI-targeted biopsy following mpMRI for men with PIRADS 3, or 4-5 lesions. Due to uncertainty or unavailability of evidence of the benefits of omitting a systematic biopsy i.e., ISUP grade 1 undetected and reduction in post-biopsy complications, the overall certainty of evidence was rated down from high to moderate, and given shared decision-making incorporating patient values and preferences is essential to our proposed recommendations, the strength of the recommendations is "conditional" (which is the preferred term by GRADE in Australia; also termed "weak" in international settings).
Screening interval of two years is largely based on the large screening effect in the Swedish component of the ERSPC trial. However, the Swedish part of the trial differed also in other respects and several efforts to disentangle the reasons for the differences between the ERSPC centers have not been able to pinpoint to a clear explanation. On the other hand, joint analyses indicate that the magnitude of mortality reduction and extent of overdiagnosis are closely correlated. Therefore, shortening the screening interval very likely also increases overdiagnosis. I would regard the evidence for selecting the screening interval as weak.	The ratings of the body of the evidence for this recommendation are found in the evidence to decision table for this clinical question and followed the pre-specified process for arriving at this recommendation. Based on the recommended GRADE protocol, the certainty of the evidence was assessed as high. The Working Group determined that for the recommended PSA testing protocol there were substantial net benefits ie the benefits outweighed the harms, and that there was no substantial variability in the values and preferences of men who have been informed of the benefits and harms of PSA testing. Based on these rating 14/15 Working Group members agreed that the recommendation be strong rather than conditional.
PI-RADS 3 findings at MRI represent a grey area, reflecting often uncertainty of the radiologist. Use of a secondary or reflex test such as PSA density seems optimal despite limited evidence. I fully agree that the evidence demonstrates the lack of value from digital rectal examination. I also find the rationale for repeating the PSA determination if the initial result is ≥3 ng/ml justified. Yet, for PSA ≥10 ng/ml this may not be necessary.	Noted, with thanks.

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The guideline emphasizes an increased prostate cancer mortality in men with affected first degree relatives. However, the evidence for this is based on data from the pre-PSA era. Several recent publications have actually shown no difference or better prognosis for men with a family history of prostate cancer. On the other hand, I share the view that for men with inherited mutations in BRCA2 and other DNA repair genes, cancers are more aggressive and prostate cancer mortality is elevated.	Noted, with thanks. Monitoring research into genetic testing is a Guidelines Research Priority (RP.3) including population-based testing for genetic mutations, polygenic risk score, genetic screening, familial syndromes, germline mutations, and the impact of genetic testing on risk stratifications and overtreatment.
Randomized trials (PCPT and REDUCE) and have shown a lower risk of prostate cancer for men using 5-ARI, with suggestive evidence also for lower mortality. I think it would be logical to suggest less screening for this group, analogous to the recommended more intensive screening for high-risk groups.	Risk reduction in these trials has only been shown for low-risk prostate cancer, but potential for increased detection of high-grade cancers.
Active surveillance is, and should be, the primary option for managing low-risk cases and some moderate-risk cases. The evidence for limiting AS to cases with PI-RADS 3 or less seems thin at best. This also applies to PSAD as a criterion for AS.	8.1 Criteria for choosing active surveillance includes cases with > PI-RADS 3: **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.*