Contents

Guidelines:PSA Testing

Guidelines developed in partnership with

Prostate Cancer Foundation of Australia

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Short form summary

- **Clinical practice guidelines: PSA Testing and Early Management of Test-Detected Prostate Cancer**

Technical report

- **Administrative report**

Note: Please note that the relevant excerpt pages of the technical report are accessible in the appendix of each content page.

For further supporting documentation please email guidelines@cancer.org.au

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Appendix 5 Abbreviations and glossary

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What is in this guideline

This guideline is intended for health professionals working with middle-aged and older men who do not have any symptoms that suggest they might have prostate cancer and are considering having a prostate-specific antigen (PSA) test, or who decide to have a test after they have been informed of the benefits and harms of testing.

It makes recommendations on how best to support men in making an informed decision for or against PSA testing and on which testing protocol to recommend to men who decide in favour of testing, depending on their age and underlying risk of prostate cancer. It also makes recommendations about further investigation after an abnormal PSA test result and the early management of prostate cancer diagnosed following such investigation.

The recommendations in this guideline are intended for people with training in medicine or other health sciences. They are not intended for the general public.

What this guideline does not cover

This guideline does not recommend a population screening program for prostate cancer (a program that offers testing to all men in a certain age group who do not have prostate cancer or symptoms that suggest prostate cancer). Current evidence does not support such a program.

This guideline **does not** make recommendations about:

- whether, or how, primary care doctors should raise the topic of prostate cancer testing with their male patients
- prostate cancer treatments such as surgical procedures, radiation, chemotherapy or drug treatments
- treatments for adverse effects of prostate cancer treatment, such as urinary and bowel problems and erectile dysfunction
- the management of advanced prostate cancer.

This guideline **does not** provide:

- detailed guidance on how individual men can make informed decisions about PSA testing or health care that follows it, or how health professionals can facilitate these choices.[i] Development of a decision aid is underway.
- a full review of factors that may increase risk of prostate cancer sufficiently to justify a PSA testing protocol different from that offered to men at average risk of prostate cancer. Guidance based on such reviews will be included in future editions of this guideline.

- information that would assist men and their doctors to assess men's expectation of life in the context of deciding whether to initiate or continue PSA testing, or to offer and accept definitive treatment for prostate cancer. Development of a calculator tool based on Australian data is underway.

Footnote

[i] NHMRC's document PSA testing for prostate cancer in asymptomatic men: information for health practitioners provides a summary of the evidence on the benefits and harms of testing for use by health practitioners before they discuss the PSA test as part of a medical consultation (NHMRC. Information for health practitioners. Canberra: NHMRC, 2014. Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/men4d_psa_testing_asymptomatic_men_140304.pdf). A decision tool is being developed to assist doctors to facilitate informed choice for or against testing.

Active surveillance

For men with biopsy-diagnosed 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 definitive treatment?

(PICO[i] question 9)

For men with biopsy-diagnosed 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? (PICO question[i] 10)

Management options for low-risk biopsy-diagnosed prostate cancer include immediate definitive treatment and active surveillance. Developing an effective management approach therefore involves:

- determining the appropriate criteria for choosing active surveillance in preference to definitive treatment for men with biopsy-diagnosed prostate cancer
- identifying the optimal monitoring protocol for active surveillance, including criteria for intervention.

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Conservative strategies for managing biopsy-diagnosed prostate cancer when cure is not the goal (watchful waiting) are discussed in Chapter 5 Watchful waiting.

Contents

Background

Active surveillance[ii] entails close follow-up of patients diagnosed with low-risk prostate cancer. The objective is to avoid unnecessary treatment of men with indolent cancer and treat only those who show signs of disease progression, so as to avoid treatment-related effects that may reduce quality of life. Definitive treatment is offered at a time when disease progression is detected and cure is deemed possible.

The optimal protocol for active surveillance is uncertain. Monitoring usually involves prostate-specific antigen (PSA) testing, digital rectal examination (DRE), prostate biopsies, and, in specialised centres, consideration of multiparametric prostate magnetic resonance imaging (MRI). There is a lack of evidence about the optimal frequency of monitoring and the most appropriate triggers for intervention. Whilst many active surveillance protocols have been reported in the literature, these vary in their inclusion criteria and monitoring procedures. To date, these active surveillance protocols have not been validated in randomised controlled trials. More importantly, they have not been examined with respect to overall and/or prostate cancer-specific mortality rates.

Evidence

Criteria for selecting active surveillance

No published randomised controlled trials were identified that compared immediate definitive treatment with active surveillance and met inclusion criteria. However, several relevant randomised controlled trials are currently underway (see Studies currently underway). The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Three cohort studies[1][2][3] at high risk of bias reported mortality and quality-of-life outcomes in men who underwent either surveillance or immediate treatment. These studies demonstrated similar prostate cancer-specific survival rates for men with prostate cancer managed by active surveillance. In all but one study,[1] men were aged greater than 50 years.

In a prospective cohort study[2] in men aged 50–80 years with PSA ≤ 20 ng/mL, clinical stage T1c prostate cancer, 1–2 cores involved and Gleason score ≤ 6,[iii] no difference in prostate cancer-specific mortality rate was demonstrated between the immediate treatment and active surveillance groups after 2.8–4.8 years of follow-up. In a prostate cancer register cohort[1] of men with PSA < 20 ng/mL, Gleason score ≤ 6, and T1–2 cancer, a slightly higher prostate cancer-specific mortality rate was observed after a median follow-up period of 8.2 years in those who underwent active surveillance than in those who received immediate treatment (0.9% versus 0.7%, $p > 0.05$). Prostate cancer-specific mortality rates were low, both overall (13.6%) and among those men aged ≥ 66 years with Gleason score ≤ 6, and clinical stage T1–2 tumours.[3]

A systematic review of prognostic factors that may identify men most suitable for active surveillance was undertaken by the UK National Collaborating Centre for Cancer during the development of the 2014 clinical guideline for prostate cancer published by the National Institute for Health and Care Excellence (NICE).[4] The NICE review included four analyses from three studies,[5][6][7][8] all of which reported results with end points of cessation of active surveillance but did not report overall survival rates, prostate cancer-specific mortality rates or quality-of-life outcomes. Factors analysed included PSA velocity, PSA doubling time, PSA level at diagnosis, PSA density, free PSA to total PSA percentage (free-to-total PSA%), total cancer length at biopsy, tumour volume, Gleason score at diagnosis, clinical stage at diagnosis, and expression of the biomarker Ki67. The single study[5] that measured PSA velocity reported that a PSA velocity greater than 1 ng/mL/year was predictive of progression ($p < 0.001$). Of the three studies that reported PSA doubling time,[6][7][8] two found it to be a significant predictor of progression.[6][8] One study[8] found that a PSA doubling time of 3 years or less was associated with an 8.5-times higher risk of biochemical progression after definitive treatment, compared with a doubling time of more than 3 years. Conflicting and inconsistent results were reported for all the other parameters.

Active surveillance protocols

Three cohort studies at high risk of bias were identified that compared immediate treatment with delayed treatment.[1][2][3] These studies reported outcomes for different combinations of prognostic and outcome variables, but did not directly compare different active surveillance protocols. Findings were inconsistent between studies.

It was not possible to make evidence-based recommendations about specific protocols for active surveillance monitoring, or triggers for intervention (see Unresolved issues).

Evidence summary and recommendations

Evidence summary	Level	References
Three cohort studies reported similar prostate cancer-specific survival rates for men aged 41–80 years with prostate cancer managed by active surveillance. In men aged ≥ 66 years with early prostate cancer with PSA ≤ 20 ng/mL, clinical stage T1–2, and Gleason score ≤ 6,[iii] active surveillance was associated with a similarly low risk of death due to prostate cancer as immediate definitive treatment.	III-2	[1], [2], [3], [5], [6], [7], [8]
A systematic review of studies that followed men undergoing active surveillance found conflicting and inconsistent results for the effects of various baseline parameters including PSA velocity, PSA level at diagnosis, PSA density, free-to-total PSA%, PSA doubling time, total cancer length at biopsy, tumour volume, Gleason score at diagnosis, clinical stage at diagnosis, and Ki67 expression. However, PSA velocity > 1.0 ng/mL/year predicted progression from active surveillance to definitive treatment ($p < 0.001$) in one study.	II, III-3	[4], [5], [6], [7], [8]
No studies were found that compared different active surveillance monitoring protocols.	N/A	

N/A: Non-applicable

Evidence-based recommendation?	Grade
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.	**C**

Consensus-based recommendation?

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.

For men aged less than 60 years, consider offering active surveillance based on the above criteria, provided that the man understands that treatment in these circumstances may be delayed rather than avoided.

Consensus-based recommendation?

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.

If the man strongly prefers active surveillance, offer repeat biopsy to ensure that disease classification is accurate.

Consensus-based recommendation?

Consider offering definitive treatment to 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.

Consensus-based recommendation?

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.

Consensus-based recommendation?

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.

Consensus-based recommendation?

During active surveillance, offer definitive treatment if pathological progression is detected on biopsy, or if the patient prefers to proceed to intervention.

Practice point?

Advise men with low-risk prostate cancer that, if they choose active surveillance, their risk of death due to prostate cancer over the next 10 years would be low, and would probably be no greater than if they were to choose immediate definitive treatment.

Practice point?

When considering active surveillance, take into account other factors that may be associated with risk of future pathological progression but for which evidence is inconsistent (e.g. total cancer length at biopsy, tumour volume, PSA doubling time < 3 years and PSA density).

Practice point?

In centres where staff have skills and experience in the use of multiparametric MRI for prostate examination, consider using it to help identify foci of potentially higher-grade disease, aid targeting at reclassification biopsies and aid determination of interval tumour growth. Clinicians and other staff performing multiparametric MRI should refer to appropriate standards and guidelines for its use (Moore CM et al 2013).

Health system implications

Clinical practice

No changes to the way care is currently organised would be required for implementation of the recommendations about which men with early prostate cancer should be offered active surveillance. If this results in more men being offered active surveillance, increased capacity for follow-up clinics and PSA testing facilities may be required.

Implementation of the recommendations for monitoring protocols during active surveillance may result in an increase in biopsies.

Resourcing

The use of multiparametric MRI would be associated with additional costs.

Biopsies performed within monitoring protocols may be associated with indirect additional costs, including the cost of pathological examination, given that the recommendation for biopsy (see Chapter 3 Prostate biopsy and multiparametric MRI) requires a taking higher number of cores than is current practice for some urologists. However, biopsy-related costs may be offset if the monitoring protocol were to result in fewer biopsies.

Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

Discussion

Footnotes

[i] Clinical questions were translated into the PICO framework: population, intervention, comparator and outcome (see 'Appendix 3'.)

[ii] Active surveillance involves PSA tests every 3 months, rectal examination every 6 months, biopsies from time to time, and (in specialised centres) multiparametric MRI. If the cancer shows signs of growing, the man can have surgery or radiotherapy. In general, men with low-risk prostate cancer who choose this option instead of immediate prostate cancer treatment do not have a higher risk of dying from prostate cancer within the next 10 years. For men younger than 60 years, choosing active surveillance might just delay surgery or radiotherapy rather than avoid it.

[iii] Gleason scores less than 6 are no longer reported for prostate cancer detected in core biopsy specimens. See the Prostate Cancer (core/needle biopsy) Structured Reporting Protocol (1st edition 2014), Royal College of Pathologists of Australasia.

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Chapter 4 Active surveillance

Discussion

Unresolved issues

There are several unresolved issues about identifying men in whom active surveillance is likely to achieve the optimal balance of benefits and harms. These include:

- difficulty in estimating life expectancy
- the safety of active surveillance in men diagnosed with Gleason score 7 (3 + 4) cancer
- the role of multiparametric MRI in selecting men for active surveillance
- the role of new biomarkers including genomic and epigenetic panels in selecting men for active surveillance
- the safety of active surveillance in men younger than 60 years.

There are also several unresolved issues about patient monitoring while on active surveillance and triggers for intervention. These include:

- the frequency of PSA measurement and repeat biopsy while on active surveillance
- the role of multiparametric MRI in predicting prostate cancer progression, which might affect the way care is organised and have resource implications
- the role of PSA doubling time as a trigger for intervention, given the multiple non-malignant causes of a variable and rising PSA levels
- the potential role of new genomic and epigenetic markers in selecting men for continued active surveillance. To date, the use of such indicators remains experimental and is not considered standard of care.
- quality-of-life outcomes of different active surveillance protocols.

Studies currently underway

Several randomised controlled trials are currently underway which, when published, may help identify appropriate criteria for active surveillance. These include:

- ‘Evaluation of Four Treatment Modalities in Prostate Cancer With Low or Early Intermediate Risk’ (PREFERE) trial[1] (Germany)
- ‘Prostate Testing for Cancer and Treatment’ (ProtecT) trial[2][3] (UK)
- The ‘MRIAS’ Study: Prospective, multi-centre, observational cohort study of multi-parametric MRI in active surveillance for low risk Prostate Cancer (Australia).

Other recent studies may inform guidance for managing sexual health in men with prostate cancer.[4][5]

Future research priorities

Important unresolved questions in the selection for men for active surveillance include:

- the role of multiparametric MRI in the selection of men for active surveillance, and in their monitoring protocols
- whether decision aids can assist men and their partners in the selection of active surveillance as their treatment of choice for low risk localised cancer
- the significance of Gleason score 3 + 4 vs 4 + 3 cancers in selection for active surveillance
- the role of genomics and epigenetic biomarkers in selecting and monitoring men for active surveillance
- the psychosocial needs of men recently diagnosed with prostate cancer and starting an active surveillance protocol.

References

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Biopsy quality criteria

***For men undergoing an initial prostate biopsy how many biopsy cores, which pattern of biopsy sampling sites and which approach constitute an adequate prostate biopsy?* (PICO question[i] 7)**

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Background

Core biopsy of the prostate with histological examination is indicated when investigations undertaken after the finding of raised PSA support the suspicion of prostate cancer (see 2.5 Testing with variants of PSA to improve sensitivity after an initial total PSA ≤ 3.0 ng/mL and 2.6 Testing with variants of PSA or repeat PSA testing to improve specificity after an initial total PSA > 3.0 ng/mL).

The purpose of core biopsy is to confirm the presence of cancer. If prostate cancer is confirmed, its type, grade and likely extent within the prostate is determined before definitive treatment is considered. A traditional approach was to collect a single core biopsy from six zones of the prostate (sextant biopsy). Current clinical practice varies considerably in the number of cores collected, with multiple cores taken from these six zones and extra cores directed at different areas of the prostate.

Evidence

One systematic review,[1] seven randomised controlled trials[2][3][4][5][6][7][8][9][10][11] and 15 sequential sampling studies[12][13][14][15][16][17][18][19][7][20][21][8][9][22][23] (three[7][8][9] with sequential sampling in an intervention arm) were identified that provided evidence relevant to determining an optimal number of core biopsies, biopsy site, and surgical approach. From an initial 12,667 citations, 109 studies in 23 articles met inclusion criteria for the review (22 articles reporting one study each[2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23] and one systematic review reporting data from 87 studies[1]). The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

The systematic review[1] compared the cancer detection rates and complications of different extended prostate biopsy schemes for diagnostic evaluation in men scheduled for biopsy. It reported that 'the standard sextant scheme has a significantly lower cancer yield than most of the more extensive biopsy schemes. As the number of cores increases, the yield improves for most of the schemes.' However, the review did not determine an optimal biopsy number and did not disentangle the independent effects of increasing core numbers and biopsy location.

Studies published since the systematic review examined a diversity of proposed schemes and comparisons. We performed a patient-level regression analysis using data from nineteen additional studies that compared various biopsy protocols.[12][13][14][4][15][5][6][16][17][19][7][20][21][8][9][10][11][22][23] Across the included studies, 23,822 biopsy components from 8,221 men were assessed for all cancers and 9,851 biopsy components from 3,701 men were assessed for cancers with Gleason score greater than 6.

Number of cores

For any given biopsy region or set of regions, men who had 24 cores taken had nearly double the odds of having cancer detected than men who had six cores taken (odds ratio [OR] 1.98; 95% confidence interval [CI] 1.52–2.58). There was also a clinically significant increase in cancer detection rate between 12 biopsies (45.6%) and 24 biopsies (56.9%) for populations in which the 6-core sextant scheme was predicted to yield 40%.

Evidence for adverse event rates was limited. It was not possible to compare rates of adverse events between groups who underwent biopsy with different numbers of cores.

Site of cores sampled

For a given number of cores, taking samples from the peripheral zones (i.e. the lateral peripheral zone [LPZ] and /or the mid-peripheral zone [MPZ]) yielded more cancers than taking samples from the transitional zone. The relative increases in yield from increasing core numbers was similar for higher-grade (Gleason score > 6) cancers and all cancers. Overall, the evidence did not show that, for a given number of cores, sampling regions in addition to the peripheral zones (i.e. LPZ and/or MPZ) led to increases in cancer yield.

Evidence for adverse event rates was limited. It was not possible to compare rates of adverse events between groups who underwent biopsy with different sampling sites.

Biopsy approach

There was insufficient evidence to determine if the transperineal approach was superior to the transrectal approach for cancer detection. None of the included studies measured concordance between biopsy and post-prostatectomy histopathology in individual patients.

Two studies[3][11] directly compared adverse events in men who underwent 12-core biopsy using the transperineal and transrectal approaches. In one study,[3] the perineal approach was associated with a significantly higher rate of headaches. Neither reported differences in other adverse events, including fever and sepsis (reported in one study).[3] Neither study reported infection rates.

Evidence summary and recommendations

Evidence summary	Level	References
Detection of prostate cancer Increasing biopsy core number improves cancer yield; as the number of cores increases, the yield increases. A patient-level regression analysis showed that: ■ for any given biopsy region or set of regions, men who have 24 cores taken had nearly double the odds of having cancer detected than men who had 6 cores taken ■ the 24-core biopsy had a clinically significant greater diagnostic yield of 56.9%, compared with 45.6% for a 12 core biopsy and an expected yield of 40% for a 6-core biopsy. For a given number of cores, taking samples from the peripheral zones (i.e. LPZ and/or MPZ) yielded more cancers than the transitional zone.	I	[12], [13], [1], [14], [4], [15], [5], [6], [16], [17], [19], [7], [20], [21], [8], [9], [10], [11], [22], [23]
Detection of prostate cancer	I	[12], [13], [14], [4], [15],

Evidence summary	Level	References
There is insufficient evidence to determine if the transperineal approach is superior to the transrectal approach in detecting cancer.		[5], [6], [16], [17], [19], [7], [20], [21], [8], [9], [10], [11], [22], [23]
Detection of cancer with Gleason score > 6 The relative increases in yield from increasing core numbers was similar for higher-grade cancers (Gleason score > 6) and all cancers. Overall, the evidence did not show that, for a given number of cores, sampling regions in addition to the peripheral zones (i.e. LPZ and/or MPZ) led to either an increase or a decrease in yield of cancers with Gleason score > 6. There is insufficient evidence to determine if the transperineal approach is superior to the transrectal approach in detecting cancers with Gleason score > 6.	I	[7], [20], [21], [8], [9], [10]
Adverse events Evidence on adverse events is limited. Differences in adverse event rates were not consistently associated with the number of core biopsies or with the biopsy pattern.	II	[1], [4], [5], [6], [7], [9], [10]
Adverse events There is insufficient evidence to determine whether the transperineal approach is consistently associated with a lower rate of adverse events than the transrectal approach.	II	[3], [11]

Evidence-based recommendation[?]	Grade
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.	**B**

Practice point?

Before offering biopsy after an elevated total PSA test result, take into account a man's family history of prostate cancer (see Chapter 1 Risk) and the results of further investigations (see 2.5 Testing with variants of PSA to improve sensitivity after an initial total PSA ≤ 3.0 ng/mL and 2.6 Testing with variants of PSA or repeat PSA testing to improve specificity after an initial total PSA > 3.0 ng/mL).

Practice point?

Transrectal and transperineal biopsy approaches are both acceptable with respect to rates of cancer detection. The approach taken should be based on the man's wishes, the surgeon's experience, risk of sepsis and other morbidity, and practical issues such as cost and access to the necessary facilities.

Health system implications

Clinical practice

While the recommendation has already been adopted by some urologists, some routinely collect fewer biopsy samples. Accordingly, implementation of the recommendation would result in an increased number of core biopsies per patient, which could increase morbidity and infection rates.

Implementation of this recommendation may result in prostate biopsy becoming a procedure that is mainly performed in operating theatres and with general anaesthesia.

Resourcing

Implementation of this recommendation would result in a small increase in the time needed to perform biopsies and a modest increase in pathology costs. No changes in equipment would be needed unless transperineal biopsy with template is considered.

Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

Footnote

[i] Clinical questions were translated into the PICO framework: population, intervention (or exposure), comparator and outcome (see Appendix 3).

References

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Appendix 2 Committee members and contributors

Appendix 2 Committee members and contributors

PCFA and Cancer Council Australia have appointed a designated Project Steering Committee. The Project Steering Committee was responsible for the overall management and strategic leadership of the guideline development process.

Guidelines developed in partnership with

Prostate Cancer Foundation of Australia

Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

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Contents

Project steering committee

Name	Position	Project role
Emeritus Professor Villis Marshall AC	Consultant Urologist; Chair, Australian Commission on Safety and Quality in Health Care, NSW	Chairman of Expert Advisory Panel
Professor Sanchia Aranda	Chief Executive Officer, Cancer Council Australia, NSW (from 3 August 2015)	Co-convenor of Expert Advisory Panel (from 3 August 2015) Project governance
Professor Bruce Armstrong AM	Emeritus Professor, School of Public Health, The University of Sydney, NSW	Expert advisor in public health Project governance
Professor Mark Frydenberg	Head of Urology, Monash Medical Centre, Southern Health, VIC	Expert advisor in urology medicine Project governance
Professor Paul Glasziou	Professor of Evidence Based Medicine, Bond University, QLD	Expert advisor in evidence base medicine Project governance
A/Professor Anthony Lowe	Chief Executive Officer, Prostate Cancer Foundation of Australia, NSW	Project Convenor Co-convenor of Expert Advisory Panel Project governance
Professor Dianne O'Connell	Senior Epidemiologist, Cancer Research Division, Cancer Council NSW	Expert advisor in epidemiology Project governance
Professor Ian Olver AM	Chief Executive, Cancer Council Australia, NSW (until 31 December 2014) Director, Sansom Institute, Chair of Translational Cancer Research, University of South Australia (from 23 February 2015)	Co-convenor of Expert Advisory Panel (until 31 December 2014) Project governance
David Sandoe OAM	National Chairman, Prostate Cancer Foundation of Australia, NSW (retired as National Chairman on 31 March 2015)	Consumer representative Project governance

Project staff

Name	Position	Project role
Julie Sykes*	Director of Health and Education Programs, Prostate Cancer Foundation of Australia	Project manager NHMRC point of contact Project governance

Name	Position	Project role
Dr Tim Wong**	Manager, Advocacy and Resources, Prostate Cancer Foundation of Australia	Project manager Project governance
Christine Vuletich***	Manager Clinical Guidelines Network, Cancer Council Australia	Management of guideline development process Project governance
Jutta von Dincklage****	Head Clinical Guidelines Network, Cancer Council Australia	Management of guideline development process Project governance Technical development and support for the online guideline development
Laura Wuellner*****	Project Manager, Clinical Guidelines Network, Cancer Council Australia	Project support
Suzy Hughes	Project Coordinator, PSA testing guidelines, Cancer Council Australia	Systematic review team
Dr Dana Stefanovic	Project Coordinator, PSA testing guidelines, Cancer Council Australia	Systematic review team
Dr Albert Chetcuti	Project Coordinator, PSA testing guidelines, Cancer Council Australia	Systematic review team
Tracy Tsang******	Project Assistant, PSA testing guidelines, Cancer Council Australia	Systematic review team
Cindy Peng	Project Assistant, PSA testing guidelines, Cancer Council Australia	Systematic review team
Katherine Sheridan	Project Assistant, PSA testing guidelines, Cancer Council Australia	Systematic review team
Sam Egger	Bio Statistician, Cancer Council NSW	Performed statistical analysis for meta-analysis on question 7
Jennifer Harman	Medical writer, Meducation	Editorial consultant

* until 3 July 2014

** until 6 October 2014

*** until 3 July 2014

**** from 4 July 2014, involved as Product Manager, Wiki Development from 2012 to 3 July 2014

***** from 3 September 2014

****** until 14 November 2014

An Expert Advisory Panel comprising of representatives from all specialities involved in the diagnosis and management of men affected by prostate cancer, and consumer representatives, was convened to develop this PSA testing guideline.

The Expert Advisory Panel is working in partnership with the systematic review team on specific clinical questions in keeping with their area of practice. Question Specific Working Parties were convened as required to develop the response to individual questions. The lead author for the individual question co-opted additional experts for this purpose using members of the Expert Advisory Panel as appropriate. The Program Steering Committee sought additional expert consultation during this process, subject to prior approval by the Expert Advisory Panel.

Expert advisory panel

Name	Position	Specialty
Emeritus Professor Villis Marshall AC, Chair Expert Advisory Panel	Consultant Urologist; Chair, Australian Commission on Safety and Quality in Health Care, NSW	Urology
Professor Sanchia Aranda	Chief Executive Officer, Cancer Council Australia, NSW (from 3 August 2015)	Cancer Control
Professor Bruce Armstrong AM	Emeritus Professor, School of Public Health, The University of Sydney, NSW	Epidemiology
Dr Joseph Bucci	Radiation Oncologist, Prostate Cancer Institute, St George Hospital, NSW	Prostate Brachytherapy
Professor Suzanne Chambers	Professor of Preventative Health, Griffith Health Institute, QLD	Psycho-oncology
A/Professor Pauline Chiarelli JP	School of Health Sciences (Physiotherapy), The University of Newcastle, NSW	Rehabilitation
Professor Chris Del Mar	Professor of Public Health, Bond University, QLD	General Practice
Professor Mark Frydenberg	Chairman, Department of Urology, Monash Medical Centre, Southern Health, VIC	Urology
Professor Robert ‘Frank’ Gardiner AM	Centre for Clinical Research, University of Queensland, QLD	Urology
Professor Paul Glasziou	Professor of Evidence Based Medicine, Bond University, QLD	General Practice
Dr Keen-Hun Tai	Chair, Faculty of Radiation Oncology Genito-Urinary Group, VIC	Radiation Oncology
A/Professor Anthony Lowe	Chief Executive Officer, Prostate Cancer Foundation of Australia, NSW	Cancer Control
Dr David Malouf	Consultant Urologist, Prostate Cancer Institute, St George Hospital, NSW	Urology
A/Professor Paul McKenzie	Senior Staff Specialist Tissue Pathology and Diagnostics, Royal Prince Alfred Hospital, NSW	Pathology

Name	Position	Specialty
Professor Robert McLachlan	Director, Andrology Australia, VIC	Male Reproductive Health
Professor Dianne O'Connell	Senior Epidemiologist, Cancer Research Division, Cancer Council NSW	Epidemiology
Professor Ian Olver AM	Chief Executive, Cancer Council Australia, NSW (until 31 December 2014) Director, Sansom Institute, Chair of Translational Cancer Research, University of South Australia (from 23 February 2015)	Cancer Control
Dr Ian Roos OAM	Consumer Advocate, Cancer Voices Australia, VIC	Consumer Advocacy
Mr David Sandoe OAM	National Chairman Prostate Cancer Foundation of Australia, NSW (retired as National Chairman on 31 March 2015)	Consumer Advocacy
A/Professor Ken Sikaris	Director of Chemical Pathology, Melbourne Pathology, VIC	Pathology
Professor Martin Stockler	Oncology and Clinical Epidemiology Medicine, Central Clinical School, The University of Sydney, NSW	Medical Oncology
Professor Phillip Stricker AO	Consultant Urologist, St Vincent's Clinic, NSW	Urology
Mr Peter Teiermanis	Consumer, Frankston, VIC	Consumer Advocacy
Ms Elizabeth Watt	Head, Clinical School of Nursing at Austin Health, School of Nursing & Midwifery, La Trobe University, VIC	Nursing
Professor Simon Willcock	Professor of General Practice, The University of Sydney, NSW	General Practice

Question Specific Working Party members and contributors

RISK

For Australian men, has a family history of prostate cancer been shown to be reliably associated with a 2.0-fold or greater increase in risk of occurrence of or death from prostate cancer when compared to men who do not have a family history of prostate cancer? (PICO question 1)

Name	Position	Speciality
Professor Bruce Armstrong AM*	Emeritus Professor, School of Public Health, The University of Sydney, NSW	Epidemiology
Professor Dianne O' Connell	Senior Epidemiologist, Cancer Research Division, Cancer Council NSW	Epidemiology

A/Professor David Smith	Research Fellow, Cancer Council NSW	Epidemiology

TESTING

In men without evidence of prostate cancer does a decision support intervention or decision aid compared with usual care improve knowledge, decisional satisfaction, decision-related distress and decisional uncertainty about PSA testing for early detection of prostate cancer? (PICO question 2)

Name	Position	Speciality
Professor Suzanne Chambers*	Professor of Preventative Health, Griffith Health Institute, QLD	Psycho-oncology
A/Professor Pauline Chiarelli JP	School of Health Sciences (Physiotherapy), The University of Newcastle, NSW	Rehabilitation
Professor Robert 'Frank' Gardiner AM	Centre for Clinical Research, University of Queensland, QLD	Urology
A/Professor Dragan Ilic	A/Professor, Department of Epidemiology and Preventive Medicine School of Public Health and Preventive Medicine Monash University, VIC	Epidemiology
Dr Walid Jammal	General Practitioner, NSW	General Practice
Dr David Latini	Assistant Professor of Urology, Baylor College of Medicine, Texas, USA	Urologist
Dr Stefano Occhipinti	Senior Lecturer, Griffith Health Institute, Behavioural Basis of Health Program, and School of Applied Psychology Griffith University, QLD	Psychology

For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality or the incidence of metastases at diagnosis and offer the best balance of benefits to harms of testing? (PICO question 3.1)

Name	Position	Speciality
Professor Bruce Armstrong AM*	Emeritus Professor, School of Public Health, The University of Sydney, NSW	Epidemiology
Professor Dallas English	Professor & Director, Centre for Molecular, Environmental, Genetic and Analytic (MEGA) Epidemiology, Melbourne School of Population and Global Health, The University of Melbourne	Epidemiology
Professor Paul Glasziou	Professor of Evidence Based Medicine, Bond University, QLD	General Practice
Dr Michael Caruana	Research Fellow, Lowy Cancer Research Centre, Prince of Wales Clinical School, NSW	Cancer Modelling
Dr Yoon-Jung Kang	Research Fellow, Lowy Cancer Research Centre, Prince of Wales Clinical School, NSW	Cancer Modelling

For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies with or without DRE perform best in detecting any prostate cancer or high grade prostate cancer diagnosed in biopsy tissue? (PICO question 3.2)		
Name	**Position**	**Speciality**
Professor Bruce Armstrong AM*	Emeritus Professor, School of Public Health, The University of Sydney, NSW	Epidemiology
Professor Paul Glasziou	Professor of Evidence Based Medicine, Bond University, QLD	General Practice
For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer does a PSA level measured at a particular age in men assist with determining the recommended interval to the next PSA test? (PICO question 3.3)		
Name	**Position**	**Speciality**
Professor Bruce Armstrong AM*	Emeritus Professor, School of Public Health, The University of Sydney, NSW	Epidemiology
Professor Dallas English	Professor & Director, Centre for Molecular, Environmental, Genetic and Analytic (MEGA) Epidemiology, Melbourne School of Population and Global Health, The University of Melbourne	Epidemiology
Professor Paul Glasziou	Professor of Evidence Based Medicine, Bond University, QLD	General Practice
For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what is the incremental value of performing a digital rectal examination (DRE) in addition to PSA testing in detecting any prostate cancer? (PICO question 4)		
Name	**Position**	**Speciality**
Professor Paul Glasziou*	Professor of Evidence Based Medicine, Bond University, QLD	General Practice
Professor Villis Marshall AC	Consultant Urologist	Urology
For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, how many years after the start of PSA testing is the benefit of PSA testing apparent? (PICO question 5)		
Name	**Position**	**Speciality**
Professor Robert 'Frank' Gardiner AM*	Centre for Clinical Research, University of Queensland, QLD	Urology
Dr Jeremy Grummet	Consultant Urologist, Australian Urology Associates, VIC	Urology
Professor James Kench	Consultant Pathologist, Royal Prince Alfred Hospital, NSW	Pathology
Dr Bruce Kynaston	Consumer advocate, Prostate Cancer Foundation of Australia	Consumer Advocacy

A/Professor David Smith	Research Fellow, Cancer Council NSW	Epidemiology
Professor Simon Willcock	Professor of General Practice, The University of Sydney, NSW	General Practice
A/Professor Scott Williams	Consultant Radiation Oncologist, Peter MacCallum Cancer Centre, VIC	Radiation Oncology

Free-to-total PSA %

For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring free-to-total PSA percentage improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single total PSA result above 3.0 ng /mL? (PICO question 6.1 a)

For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring free-to-total PSA percentage improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL? (PICO question 6.1 b)

PSA velocity

For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring PSA velocity improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL? (PICO question 6.2 a)

For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring PSA velocity improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL? (PICO question 6.2 b)

Prostate Health Index (PHI)

For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring the Prostate Health Index (PHI) improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL? (PICO question 6.3 a)

For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring the Prostate Health Index (PHI) improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single elevated total PSA result above 3.0 ng/mL? (PICO question 6.3 b)

Repeated total PSA

For asymptomatic men with initial total PSA above 3.0 ng/mL, does repeating the total PSA test and using an initial and repeat total PSA above 3.0 ng/mL as the indication for biopsy, improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL as the indication for biopsy? (PICO question 6.4)

Name	Position	Speciality
A/Professor Ken Sikaris*	Director of Chemical Pathology, Melbourne Pathology, VIC	Pathology
Professor Villis Marshall AC*	Consultant Urologist	Urology
Dr David Malouf	Consultant Urologist, Prostate Cancer Institute, St Georges Hospital, NSW	Urology

PROSTATE BIOPSY AND MULTIPARAMETRIC MRI

For men undergoing an initial prostate biopsy how many biopsy cores, which pattern of biopsy sampling sites and which approach constitute an adequate prostate biopsy? (PICO question 7)

Name	Position	Speciality
Professor Villis Marshall AC*	Consultant Urologist	Urology
A/Professor Paul McKenzie*	Senior Staff Specialist Tissue Pathology and Diagnostics, Royal Prince Alfred Hospital, NSW	Pathology
Professor Bruce Armstrong AM	Emeritus Professor, School of Public Health, The University of Sydney, NSW	Epidemiology

In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy? (PICO question 8.1)

In men with suspected prostate cancer whose initial TRUS biopsy is negative, what should be the next investigation(s)? (PICO question 8.2)

Name	Position	Speciality
Professor Robert 'Frank' Gardiner AM*	Centre for Clinical Research, University of Queensland, QLD	Urology
Professor Suzanne Chambers	Professor of Preventative Health, Griffith Health Institute, QLD	Psycho-oncology
Professor Paul Glasziou	Professor of Evidence Based Medicine, Bond University, QLD	General Practice
A/Professor Nathan Lawrentschuk	Consultant Urologist, University of Melbourne; Department of Surgery, Austin Hospital, VIC	Urology
Professor Phillip Stricker AO	Consultant Urologist, University of Melbourne; Department of Surgery, Austin Hospital, VIC	Urology
Dr Keen-Hun Tai	Chair, Faculty of Radiation Oncology Genito-Urinary Group, VIC	Radiation Oncology
Professor James Kench	Consultant Pathologist, Royal Prince Alfred Hospital, NSW	Pathology

ACTIVE SURVEILLANCE

For men with biopsy-diagnosed 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 definitive treatment? (PICO question 9)

Name	Position	Speciality
Professor Mark Frydenberg*	Chairman, Department of Urology, Monash Medical Centre, Southern Health, VIC	Urology
Professor Phillip Stricker AO*	Consultant Urologist, St Vincent's Clinic, NSW	Urology

For men with biopsy-diagnosed 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? (PICO question 10)

Name	Position	Speciality
Professor Mark Frydenberg*	Chairman, Department of Urology, Monash Medical Centre, Southern Health, VIC	Urology
Professor Phillip Stricker AO*	Consultant Urologist, St Vincent's Clinic, NSW	Urology

WATCHFUL WAITING

For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does watchful waiting achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment? (PICO question 11)

Name	Position	Speciality
Professor Robert 'Frank' Gardiner AM*	Centre for Clinical Research, University of Queensland, QLD	Urology
Dr Jeremy Grummet	Consultant Urologist, Australian Urology Associates, VIC	Urology
Professor James Kench	Consultant Pathologist, Royal Prince Alfred Hospital, NSW	Pathology
Dr Bruce Kynaston	Consumer advocate, Prostate Cancer Foundation of Australia	Consumer Advocacy
A/Professor David Smith	Research Fellow, Cancer Council NSW	Epidemiology
Professor Simon Willcock	Professor of General Practice, The University of Sydney, NSW	General Practice
A/Professor Scott Williams	Consultant Radiation Oncologist, Peter MacCallum Cancer Centre, VIC	Radiation Oncology

For men with prostate cancer following a watchful waiting 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? (PICO question 12)		
Name	**Position**	**Speciality**
Professor Phillip Stricker AO*	Consultant Urologist, St Vincent's Clinic, NSW	Urology
Professor Martin Stockler*	Oncology and Clinical Epidemiology Medicine, Central Clinical School, University of Sydney (NSW)	Medical Oncology

*Lead author

Acknowledgements

- This guideline is dedicated to the memory of Dr Ian Roos OAM, who passed away on 10 April 2015 after a long battle with prostate cancer. Ian was a scholar, scientist, administrator, educator, guide, philosopher and friend of Cancer Council Australia and Prostate Cancer Foundation of Australia. His work as a consumer representative, patient advocate and policy advisor, since his diagnosis with an aggressive prostate cancer 16 years ago, set him apart. Dr Roos will be greatly missed.
- Cancer Council NSW for its in kind support for performing the statistical analysis of question 7 by Sam Egger.
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- Annette Pflugfelder MD, PhD Student, Dermatology Research Centre at The University of Queensland and Kelvin Hill, National Manager Clinical Programs, for assessing the draft guidelines with the AGREE II instrument.
- Yaping Liu, Librarian at Cancer Council NSW for helping to collect references.
- Charley Wang, intern at Cancer Council Australia for helping to collect full text of articles.

Conflict of interest register

Appendix 6 Conflict of interest register

Guidelines developed in partnership with

Prostate Cancer Foundation of Australia

Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

Published: 2015

National Health and Medical Research Council

Decision support for men considering PSA testing

In men without evidence of prostate cancer does a decision support intervention or decision aid compared with usual care improve knowledge, decisional satisfaction, decision-related distress and decisional uncertainty about PSA testing for early detection of prostate cancer? **(PICO[i] question 2)**

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Contents

Background

Decision support interventions and/or decision aids aim to help people make an informed decision about testing or treatment by providing information about the benefits, harms, limitations and uncertainty associated with the choice. They are defined as interventions designed to help people make specific and deliberative choices among options (including the status quo) by providing, at a minimum, both information on the options and outcomes relevant to a person's health status, and implicit methods to clarify values.[1] Decision support interventions /decision aids may be implemented in a variety of formats, including written hardcopy (e.g. pamphlet/booklet), multimedia (e.g. computer, DVD, internet-based), or in person (e.g. counselling by nurse or physician).[1]

Evidence

A total of 13 randomised controlled trials (eight[2][3][4][5][6][7][8][9] at high risk of bias and five[10][11][12][13][14] at moderate risk of bias) examined the impact of decision support interventions and/or decision aids for men making a decision whether to undergo PSA testing for early detection of prostate cancer. The comparator was information only in six studies,[4][8][6][10][12][9] usual care in two studies,[5][7] and no intervention in five studies.[2][3][11][13][14] The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

The majority of the 13 randomised controlled trials demonstrated that the use of decision support interventions and/or decision aids was associated with a significant improvement in patient knowledge[2][3][4][5][10][11][12][13][7][14][8] and a significant reduction in patient decision-related distress (anxiety and reported worry about developing prostate cancer and/or death from prostate cancer, as measured by the Decisional Conflict Scale).[3][4][5][10][11][13][9][7][8][14] Of the five randomised controlled trials that measured men's satisfaction about their decision-making, three reported significant increases in satisfaction.[4][6][7] Of the four studies that measured men's uncertainty about the decision (using the uncertainty subscale of Decisional Conflict Scale),[4][10][9][14] none demonstrated decreases in uncertainty.

Evidence summary and recommendations

Evidence summary	Level	References
Use of a decision support intervention/decision aid, compared with usual care or minimally enhanced usual care, improved men's knowledge about the benefits and harms of PSA testing.	II	[2], [3], [4], [10], [11], [12], [5], [13], [6], [14], [9], [8], [7]
Use of a decision support intervention/decision aid, compared with usual care or minimally enhanced usual care, decreased the decisional conflict/distress men experienced when considering the benefits and harms of PSA testing.	II	[2], [3], [4], [10], [11], [12], [6], [9], [8], [7]
Use of a decision support intervention/decision aid, compared with usual care or minimally enhanced usual care, improved men's satisfaction with their choice about whether or not to undertake a PSA test.	II	[4], [6], [7], [9], [10]
Use of a decision support intervention/decision aid, compared with usual care or minimally enhanced usual care, had no demonstrable benefit on the decisional uncertainty men experienced when considering the benefits and harms of PSA testing.	II	[4], [9], [10], [14]

Evidence-based recommendation[?]	Grade
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.	**C**

Practice point[?]
Familiarity with the NHMRC fact sheet *PSA testing for prostate cancer in asymptomatic men. Information for health practitioners*, which summarises evidence on the benefits and harms of PSA testing, should help health practitioners to accurately inform men about PSA testing.

Health system implications of these recommendations

Clinical practice

Decision aids are not currently used routinely in primary care when discussing PSA testing. Usual care will need to incorporate the use of decision aids, either as part of the consultation with the main clinician (e.g. GP), a separate consultation with the primary care nurse (e.g. practice nurse) or health educator, or self-directed engagement with a decision aid.

Community-wide strategies will be needed to increase public awareness of decision aids for PSA testing and to improve their accessibility.

Some decision aids require a health professional (e.g. practice nurse or health educator) to 'coach' men. Implementing this type of decision aid would require a training program on PSA testing and counselling to be incorporated into nursing/health science courses, or upskilling of existing professionals with the appropriate skills and knowledge.

Resourcing

Decision aids are produced across a variety of modalities, yet not all are readily accessible. It will be necessary to ensure that decision aids are available in primary care and to the community.

Health professionals will need appropriate training in the use of these aids. For example, coaching or counselling of patients is a component of some decision aids.

Barriers to implementation

Perceived lack of accessibility of decision aids by health professionals and consumers may be a barrier to its implementation. If the use of decision aids is to be incorporated into consultations in general practice, limited GP time may also be a barrier for implementation. These barriers may be potentially overcome by providing greater infrastructure and partnerships between primary practice, community care and peak bodies (e.g. the Royal Australian College of General Practitioners, Cancer Council Australia).

Footnote

[i] Clinical questions were translated into the PICO framework: population, intervention (or exposure), comparator and outcome (see Appendix 3).

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Discussion

Follow-up to a negative prostate biopsy

In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy? **(PICO^{i} question 8.1)**

In men with suspected prostate cancer whose initial TRUS biopsy is negative, what should be the next investigation(s)? **(PICO^{i} question 8.2)**

Guidelines developed in partnership with

Prostate Cancer Foundation of Australia

Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

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Contents

Background

A negative prostate biopsy does not definitively exclude the presence of cancer. Men who have had one negative biopsy may still have prostate cancer. Factors that might indicate undetected prostate cancer include:

- raised PSA
- abnormal digital rectal examination (DRE)

- abnormal results of other PSA-based tests, such as free PSA to total PSA expressed as a percentage (free-to-total PSA%), PSA density and PSA velocity
- novel biomarkers, such as the prostate cancer gene 3 (*PCA3*) assessed prior to initial biopsy
- specific pathological features of the initial biopsy.

There is a trend towards the use of adjuncts to improve the cancer detection yield following a negative first transrectal ultrasound-guided (TRUS) biopsy. Sampling strategies and imaging techniques currently under investigation for improving prostate cancer diagnosis rates include:

- repeat TRUS biopsy
- multiparametric MRI or magnetic resonance spectroscopy imaging (MRSI) in combination with repeat TRUS biopsy
- extended/saturation TRUS biopsy
- three-dimensional (3D) ultrasound and biopsy
- template (perineal) biopsy
- contrast-enhanced ultrasound and biopsy
- elastography and biopsy
- review of initial biopsy histopathology.

Most of these techniques have been introduced at a local level based on facilities available, rather than according to a systematic approach. The majority of tumours are known to be in the posterior zone of the prostate, but tumours that occur in the anterior zone of the prostate are often missed with TRUS biopsies, particularly in large prostates. Sampling this area is improved with template (perineal) biopsies or with saturation biopsies. Multiparametric MRI localises the lesion(s) of interest in the prostate to permit more accurate placement of the biopsy needle. Template biopsies cannot be performed under local anaesthesia, so there are cost implications compared with transrectal biopsy or transrectal saturation biopsies under local anaesthetic.

The goals of imaging are:

- to reduce the number of patients requiring biopsy while minimising the risk of missing significant cancers
- to require fewer biopsies to be taken in men in whom significant lesions are detected. (This is an appropriate goal, provided that the treatment team is not considering offering focal therapy).

Thus, the overall aim of imaging is to lessen the rate of over-diagnosis.

Evidence

Prognostic factors that determine the need for further investigation following a negative biopsy

In developing a recent UK National Institute for Health and Care Excellence (NICE) clinical guideline for the diagnosis of treatment of prostate cancer,[1] the UK National Collaborating Centre for Cancer undertook a systematic review to identify the prognostic factors that determine the need for further investigation following a prior negative biopsy in men who have been referred with suspected prostate cancer. The review included retrospective and prospective cohort studies that reported on the following potential prognostic factors: age, ethnicity, family history of prostate cancer, DRE, total PSA, free-to-total PSA%, PSA density, PSA velocity[ii] and PCA3 score at the time of initial biopsy, and histopathological features reported on initial biopsy (high-grade prostatic intraepithelial neoplasia [PIN] or atypical small acinar proliferation [ASAP][iii]).

The NICE systematic review classified the results of relevant predictive studies into two broad groups: results of univariate analyses (no control for potential confounding) and results of multivariate analyses (some control for potential confounding). The multivariate analyses are likely to provide more reliable evidence, because they reduce the risk of bias due to confounding variables. The most frequently addressed potentially confounding variables were age, DRE, PSA, free-to-total PSA%, PSA density, PSA velocity, high-grade PIN, ASAP and prostate volume.

We updated the NICE systematic review to identify recently published studies. The search strategy, inclusion and exclusion criteria, and quality assessment for the updated NICE systematic review are described in detail in the Technical report. The updated review identified evidence from cohort studies assessing the prognostic value of an additional biomarker: hypermethylation of DNA in three marker genes (*GSTP1*, *APC* and *RASSF1*) in tissue from the initial biopsy. For other parameters of interest included in the update review, such as prostate health index, no studies met inclusion criteria (see Technical report).

The NICE review[1] rated one study as moderate quality and the remainder as low or very low quality. The main weaknesses were that, in many of the studies, the prognostic factor of interest influenced whether patients underwent repeat biopsy and that many of the models did not include important confounding factors such as age, free-to-total PSA%, and prostate volume. In the updated NICE systematic review, all the identified studies were assessed to have a high risk of bias.

Age

The NICE review[1] included 14 studies that examined the relationship of age (as a continuous variable) with risk of prostate cancer at re-biopsy, using multivariate models that adjusted for potential confounders. The review reported odds ratios (ORs) of 1.01–1.10 per year increase in age. In three studies, the relationship between age and prostate cancer risk was statistically significant ($p < 0.05$).

The updated NICE systematic review found three additional studies that included age in multivariate models. Two studies each reported ORs of 1.01 per year of age as a continuous variable ($p > 0.05$).[2][3] Another study reported an OR of 1.47 with a 95% confidence interval (CI) of 1.10–1.97 for comparison of the 75th with 25th percentiles of age as a continuous variable.[4]

Ethnicity

The NICE review[1] included one study that examined relationship of ethnic background with risk of prostate cancer at re-biopsy in a multivariate model. It reported an OR of 0.8 (95% 0.4–1.6) for men of Caucasian ethnic origin, relative to those of other ethnic origins.

The updated NICE systematic review found two additional studies that examined relationship of ethnicity with risk of prostate cancer at re-biopsy in a multivariate model. In these US cohorts, African-American men had ORs of 1.21 (95% CI 0.63–2.31)[4] and 0.58 (95% CI 0.23–1.45),[2] relative to men of non-black ethnicity.

Family history

Both of two studies included in the NICE review[1] found family history to be a significant predictor of prostate cancer at re-biopsy in multivariate models. One study reported OR 3.1 (95% CI 1.2–8.0), relative to no family history of prostate cancer.

The updated NICE systematic review found two additional studies that examined the relationship of family history with risk of prostate cancer at re-biopsy. These studies observed ORs of 1.33 (95% CI 0.81–2.18)[4] and 0.92 (95% CI 0.50–1.72)[2] in multivariate models.

Digital rectal examination

The NICE review[1] found 13 studies that examined the relationship of abnormal DRE with risk of prostate cancer at re-biopsy in multivariate models. These studies reported ORs of 0.4–6.75 for abnormal DRE relative to normal DRE. Abnormal DRE was a statistically significant predictor of prostate cancer at re-biopsy in five studies, three of which reported ORs (2.63–4.61, relative to normal DRE). Eight studies reported low overall diagnostic accuracy; most reported low sensitivity (range 0–55.9% and less than 26% in six studies) but high specificity (range 56.3–95.9% and greater than 85% in five studies).

The updated NICE systematic review found one additional study, which reported an OR of 1.36 for abnormal DRE relative to normal DRE ($p = 0.30$) in a multivariate model.[3]

Total PSA

The NICE review[1] found 14 studies that examined the relationship of PSA as a continuous variable with risk of prostate cancer at re-biopsy in multivariate models, and reported ORs of 0.93–1.04 per ng/mL increase in PSA. In three studies, total PSA was a statistically significant predictor of prostate cancer on re-biopsy. Two studies reported multivariate adjusted results for PSA in categories; neither was statistically significant. Sensitivity and specificity were not consistent for similar PSA levels in six studies and showed no clear trend with increasing PSA thresholds.

The updated NICE systematic review found two additional studies that examined the relationship of PSA with risk of prostate cancer at re-biopsy. One study reported a multivariate-adjusted OR of 1.59 for PSA < 10 relative to PSA ≥ 10 ng/mL ($p = 0.18$).[3] The other study did not report multivariate-adjusted results for PSA.[4]

Free to total PSA percentage

The NICE review[1] found eight studies of the relationship of free-to-total PSA% as a continuous variable with prostate cancer at re-biopsy examined in multivariate models, and reported ORs of 0.87–1.40 per unit increase in free-to-total PSA%. Four of these studies reported statistically significant associations; three reported inverse associations and one reported a direct association. Three reported multivariate adjusted ORs comparing categories of free-to-total PSA%. In each case the OR was less than 1 for the higher category relative to the lower category, but was not statistically significant. Sensitivity and specificity were not consistent for similar free-to-total PSA% levels between five studies and showed no clear trend with increasing cut-off level.

The updated NICE systematic review found one additional study that examined the relationship of free-to-total PSA% with risk of prostate cancer at re-biopsy,[4] but it did not report multivariate-adjusted results.

PSA density

The NICE review[1] identified five studies that reported the relationship of PSA density as a continuous or categorical variable with prostate cancer at re-biopsy examined in multivariate models, four of which reported statistically significant results. Where reported, ORs were 1.005 (95% CI 0.998–1.012) per unit of PSA density as a continuous variable, and 2.3 (95% CI 1.4–4.0) and 2.34 ($p = 0.012$) for a PSA density of > 0.15 relative to less than this value. Test performance characteristics were reported for only one study (sensitivity 66%, specificity 60%).

The updated NICE systematic review found one additional study that examined the relationship of PSA density with risk of prostate cancer at re-biopsy,[4] but it did not report multivariate-adjusted results.

PSA velocity

The NICE review[1] found five studies that examined the relationship of PSA velocity as a continuous or categorical variable with risk of prostate cancer at re-biopsy in multivariate models. Three of these reported statistically significant results. Where reported, ORs were 1.34 (95% CI 1.03–1.74) and 1.58 (95% CI 1.06–2.35) per unit of PSA velocity as a continuous variable. Sensitivity and specificity showed no clear trend with increasing cut-off level and demonstrated low overall diagnostic accuracy in four studies.

The updated NICE systematic review found no additional published results from studies that examined the relationship between PSA velocity and risk of prostate cancer at re-biopsy.

Atypical small acinar proliferation

The NICE review[1] found five studies that examined the relationship between the presence of ASAP and the risk of prostate cancer at re-biopsy in multivariate models. All reported statistically significant associations ($p < 0.05$). One study that was reported twice (more participants in the second report) reported multivariate adjusted OR of 20.7 (95% CI 4.45–96.4; $p < 0.001$) in the first report and 17.7 ($p < 0.001$) in the second. The other four studies reported ORs ranging between 2.97 and 3.65. Two studies that assessed diagnostic accuracy for the presence of ASAP at initial biopsy both reported low sensitivity but high specificity.

The updated NICE systematic review found one additional study that examined the relationship between the presence of ASAP and the risk of prostate cancer at re-biopsy. It reported an OR of 1.92 (95% CI 1.07–3.46).[4]

High-grade PIN

The NICE review[1] found eight studies that examined the relationship between the presence of high-grade PIN and the risk of prostate cancer at re-biopsy in multivariate models, and reported ORs of 0.13–3.2. Only one of these reported an OR of less than 1. Four studies reported a statistically significant relationship. Five studies reported inconsistent test performance characteristics for the presence of high-grade PIN at initial biopsy as a predictor of risk of prostate cancer at repeat biopsy.

The updated NICE systematic review found two additional studies that examined the relationship between the presence of high-grade PIN and the risk of prostate cancer at re-biopsy. These studies reported ORs of 1.87 (1.23–2.85)[4] and 1.25 ($p = 0.5$).[3]

PCA3

The NICE review[1] found three studies that reported multivariate-adjusted associations of PCA3 score with prostate cancer at re-biopsy. All reported statistically significant associations. One reported an OR of 1.02 (95% CI 1.00–1.03) per unit of PCA3 score as a continuous variable. Another reported an OR of 3.01 (95% CI 1.74–5.23) for a PCA3 score of > 30 relative to < 30. The third reported ORs of 9.44 (95% CI 5.15–17.31) and 9.29 (95% CI 5.11–16.89), respectively, for PCA3 score cut-offs of 39 and 50. In 12 studies that measured sensitivity and specificity, these were not consistent and showed no clear trend with increasing cut-off level, indicating low overall diagnostic accuracy.

The updated NICE systematic review found no additional studies that examined the relationship of PCA3 score with risk of prostate cancer at re-biopsy.

DNA methylation

The updated NICE systematic review found one study[3] that examined the relationship between hypermethylation of three marker genes (GSTP1, APC and RASSF1) evaluated in tissue from the first biopsy, and risk of prostate cancer on re-biopsy. It reported an OR of 3.17 (95% CI 1.81–5.53), adjusted for age, PSA, DRE, and histopathology of first biopsy (benign, atypical cells, high-grade PIN). The sensitivity of the test was 68% and specificity was 64%.

Choice of further investigation following a negative biopsy

In developing the NICE clinical guideline[1] for the diagnosis of treatment of prostate cancer, the UK National Collaborating Centre for Cancer undertook a systematic review to identify adjuncts following a negative first TRUS biopsy to improve cancer detection in men who have been referred with suspected prostate cancer. The review identified two systematic reviews[5][6] and one randomised controlled trial[7] of enhanced ultrasound. It also included case series studies (level IV evidence) and comparative studies.[1] Included studies reported the following tests at repeat biopsy: repeat TRUS biopsy, multiparametric MRI (or MRS) in combination with repeat TRUS biopsy, extended/saturation TRUS biopsy, 3D ultrasound and biopsy, template biopsy, contrast-enhanced ultrasound and biopsy, elastography-guided biopsy, and review of the initial biopsy histopathology.

The NICE systematic review[1] assessed the risk of bias using the QUADAS-2 checklist.[8] Namely, risk of bias in patient selection (whether the sample was representative and whether the selection criteria were clearly described) and risk of bias in the index test (whether the repeat biopsy protocol was described in sufficient detail). Risk of bias was deemed to be low in the majority of studies.[1]

The NICE systematic review[1] was updated by the Guidelines' Expert Advisory Panel (see Technical report). The updated NICE systematic review was restricted to level II evidence: studies that directly compared different investigations post negative biopsy (i.e. sequential sampling studies or randomised controlled trials). Eight additional level II evidence sequential sampling studies were found.34-41 All eight update studies were assessed to be at moderate risk of bias using a modified QUADAS-2 quality appraisal tool.[9][10][11][12][13][14][15][16] The quality assessment criteria, including those for assessing risk of bias, are described in the Technical report).

Multiparametric MRI targeted biopsy

The NICE systematic review included four level II studies[17][18][19][20] that assessed multiparametric MRI-guided biopsy in men with a previous negative biopsy undergoing repeat biopsy. These studies used repeat standard biopsy protocols that ranged from 6 to 12 cores. Among those with positive findings on multiparametric MRI imaging, adding multiparametric MRI-targeted biopsy to a repeat 12-core biopsy improved the cancer detection rate. In one study, adding multiparametric (T2W + DWI + DCE) MRI increased the cancer detection rate by 14.3 percentage points,[20] while adding multiparametric (T2W + DWI) MRI increased the cancer detection rate by 45.2 percentage points.[17]

The updated NICE systematic review identified another two studies[10][11] in which multiparametric MRI-targeted biopsy was performed in addition to a 12-core random or systematic biopsy in men with a previous negative biopsy. One reported that multiparametric (T2W + DCE) MRI improved the cancer detection rate by 6.4 percentage points,[10] while the other reported that unspecified multiparametric MRI improved the cancer detection rate by 10.1 percentage points.[11]

The updated NICE systematic review identified one study that assessed the addition of multiparametric MRI-targeted biopsy to repeat saturation biopsy.[13] It found that adding multiparametric (T2W + DWI + DCE + MRS) MRI-targeted biopsies to the saturation biopsy improved the cancer detection rate by 5.1 percentage points for all men undergoing biopsy regardless of MRI findings, and by 8.7 percentage points for the subgroup of men who underwent targeted biopsy.

There were no included studies in which all participants underwent an initial biopsy using 21–24 cores.

Enhanced ultrasound-targeted biopsy

Studies included in the NICE systematic review found that adding enhanced ultrasound targeted biopsy to TRUS grey-scale schematic biopsy resulted in cancer detection rates similar to those using the TRUS grey-scale schematic biopsy method alone. In the only relevant level II study, the addition of enhanced ultrasound (colour Doppler)-targeted biopsy to a TRUS grey-scale 13-core systematic biopsy improved the cancer detection rate by 2–3 percentage points.[1]

Saturation or extended biopsy

Studies included in the NICE systematic review found that increasing the number of biopsy cores increased cancer detection rates.[1] Transrectal 12–14 core biopsies had a cancer detection rate of 15%–25%. Transrectal saturation biopsies had a cancer detection rate of 11%–45%, and transperineal saturation biopsies had a cancer detection rate of 23%–72%.

The most common complication was haematuria, which occurred in 8.8% of men undergoing transrectal saturation biopsy and 23.4% of men undergoing transperineal biopsy.

Elastography targeted biopsy

Studies included in the NICE systematic review found no relevant evidence.[1] The updated NICE systematic review found that the addition of elastography targeted biopsies to a 10-core TRUS biopsy increased cancer detection rate by 8.2 percentage points.[16]

Review of initial biopsy

A study included in the NICE systematic review found that review of initial biopsy reclassified 1.2% of benign biopsies as cancerous and 0.4% of positive biopsies as benign.[1]

Evidence summary and recommendations

Evidence summary	Level	References
Age There is consistent evidence that each additional year of age at an initial negative biopsy predicts a 1–10% greater risk of prostate cancer at re-biopsy.	II, III-3	[1], [4], [2], [3]
Ethnicity There is consistent evidence in three studies (two including African American men) that ethnicity at an initial negative biopsy is not associated with prostate cancer at re-biopsy.	II, III-3	[1], [4], [2]
Family history of prostate cancer There is inconsistent evidence in four studies that family history of prostate cancer at an initial negative biopsy is associated with risk of prostate cancer at re-biopsy.	II, III-3	[1], [4], [2]
DRE There is moderately consistent evidence that an abnormal DRE at an initial negative biopsy predicts a higher risk of prostate cancer at re-biopsy, with high specificity but low sensitivity.	II, III-2, III-3	[1], [3]
Total PSA There is little evidence that a higher total PSA at an initial negative prostate biopsy predicts a higher risk of prostate cancer at re-biopsy.	II, III-2, III-3	[1], [4], [3]
Free to total PSA%	II, III-2, III-	[1], [4]

Evidence summary	Level	References
There is inconsistent evidence that a higher free-to-total PSA% at an initial negative prostate biopsy predicts a lower risk of prostate cancer at re-biopsy.	3	
PSA density A moderately consistent association of PSA density at an initial negative biopsy with risk of prostate cancer at re-biopsy is rendered uncertain by the few studies that adjusted for possible confounding and incomplete reporting of key results.	II, III-2, III-3	[1], [4]
PSA velocity A moderately consistent association of PSA velocity at an initial negative biopsy with risk of prostate cancer at re-biopsy is rendered uncertain by the few studies that adjusted for possible confounding and incomplete reporting of key results.	II, III-2, III-3	[1]
Atypical small acinar proliferation There is consistent evidence that a finding of ASAP at an initial negative biopsy predicts with high specificity but low sensitivity a higher risk of prostate cancer at re-biopsy.	II, III-2, III-3	[1], [4]
High-grade PIN There is moderately consistent evidence that high-grade PIN at an initial negative biopsy predicts a higher risk of prostate cancer at re-biopsy, but with low diagnostic accuracy.	II, III-2, III-3	[1], [4], [3]
PCA3 The three studies that adjusted for potential confounding found significantly positive associations of PCA3 at an initial negative biopsy with prostate cancer at re-biopsy. However, the sensitivity and specificity PCA3 for prostate cancer at re-biopsy were not consistent in 12 studies in which they were measured and showed no clear trend with increasing cut-off level.	II, III-2, III-3	[1]
DNA methylation The only available study found that methylation of three marker genes in tissue from an initial negative biopsy was a moderately strong predictor of prostate cancer at re-biopsy.	II, III-2, III-3	[3]
Multiparametric MRI-targeted biopsy	II, IV	[9], [19], [11], [12], [17], [13], [18], [10],

Evidence summary	Level	References
Studies included in the NICE systematic review found that, compared with 12-core biopsy protocols, adding multiparametric MRI (T2W+ DWI +DCE)-targeted biopsies improved cancer detection rates by 14.3 percentage points and adding T2W + DWI multiparametric MRI improved cancer detection rates by 42.6 percentage points. For men with positive findings on multiparametric MRI, adding multiparametric MRI-targeted biopsies to 12-core biopsies improved cancer detection rates by 6.4, 10.1, 14.3 and 45.2 percentage points. A single study from the updated NICE systematic review showed that a repeat saturation biopsy on its own had a cancer detection rate of 35.9%. Adding 3–4 multiparametric MRI-targeted biopsies increased the cancer detection rate by an additional 5.1 percentage points.		[14], [20], [15], [1]
Enhanced ultrasound-targeted biopsy Studies included in the NICE systematic review found that adding enhanced ultrasound targeted biopsy to TRUS grey-scale schematic biopsy resulted in cancer detection rates similar to those using the TRUS grey-scale schematic biopsy method alone.	II, IV	[1]
Saturation or extended biopsy Studies included in the NICE systematic review found that increasing the number of biopsy cores increased cancer detection rates. Transrectal 12–14 core biopsies had a cancer detection rate of 15–25%. Transrectal saturation biopsies had a cancer detection rate of 11–45%, and transperineal saturation biopsies had a cancer detection rate of 23–72%. The most common complication was haematuria, reported in 8.8% of men undergoing transrectal saturation biopsy and 23.4% of men undergoing transperineal biopsy.	IV	[1]
Elastography targeted biopsy Studies included in the NICE systematic review found no relevant evidence. NICE update review found that the addition of elastography-targeted biopsies to a TRUS 10-core biopsy increased cancer detection rate by 8.2 percentage points.	II, IV	[16], [1]
Review of initial biopsy A study included in the NICE systematic review found that review of initial biopsy reclassified 1.2 % of benign biopsies as cancerous and 0.4% of positive biopsies as benign.	IV	[1]

Note: The additional studies identified in the update review (those published after the NICE systematic review and before 1 March 2014) did not materially alter the evidence on which the recommendations in the NICE guideline[1] were based. Therefore we have chosen to adapt the NICE 2014 recommendations with minimal changes. The NICE guideline recommended that clinicians should advise men whose initial biopsy is negative for prostate cancer that there is still a risk that prostate cancer is present, and that the risk is higher if any of the following conditions apply: the initial biopsy showed high-grade prostatic intraepithelial neoplasia, the initial biopsy showed atypical small acinar proliferation, or their digital rectal examination before the initial biopsy was abnormal.

Evidence-based recommendation?	Grade
Advise men whose initial biopsy is negative for prostate cancer that they should continue to be followed. Monitor more closely men with abnormal findings on pre-biopsy digital rectal examination, and those whose biopsy findings included either atypical small acinar proliferation or high-grade prostatic intra-epithelial neoplasia. In addition to further PSA testing and digital rectal examination, consider prostate imaging with investigations that can help to localise the site of cancer within the prostate, and repeat biopsy using a targeted approach.	**D**

Evidence-based recommendation?	Grade
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. Do not offer another biopsy if the multiparametric MRI (using T2- and diffusion-weighted imaging) is negative, unless any of the following risk factors are present: ■ atypical small acinar proliferation on initial biopsy ■ abnormal digital rectal examination before the initial biopsy ■ high-grade prostatic intraepithelial neoplasia on initial biopsy.	**D**

Practice point?

Multiparametric MRI should be used only in centres with experienced radiologists appropriately trained in the use of multiparametric MRI to aid urologists in the management of individual patients.[iv]

[iv] Refer to Urological Society of Australasia position statement: Status of mp-MRI prostate 2012: report from the MRI Prostate Working Party (available at www.usanz.org.au).

Practice point?

Clinicians and other staff performing multiparametric MRI should do so in accordance with appropriate standards and guidelines for its use.[v]

[v] See Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. European urology 2013; 64: 544-552.

Practice point?

The recommendations for multiparametric MRI apply only to its use in patients who have already undergone biopsy. Primary healthcare professionals should not order multiparametric MRI in the initial investigation of suspected prostate cancer in men with raised PSA levels.

Practice point?

Advise patients not undergoing repeat biopsy after a normal multiparametric MRI that there is a 10–15% chance of missing a significant cancer and that further follow-up is recommended.

Practice point[?]

For men at average risk for prostate cancer whose initial biopsy is negative for prostate cancer, and who have a life expectancy of less than 7 years (e.g. due to their age or due to other illness), advise that no further action is recommended unless they develop symptoms that suggest prostate cancer.

Health system implications

Clinical practice

Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not necessitate significant changes to usual care or changes in the way care is organised.

The use of multiparametric MRI after an initial biopsy would affect the patient's pathway through the healthcare system and would alter the way clinical decisions are made about further biopsies.

Resourcing

Implementation of the recommendation for the use of multiparametric MRI would lead to an increase in referrals for this imaging procedure before clinical decisions are made about further biopsies and would therefore increase the cost of care, but may reduce the number of further biopsies. If a man chooses to have multiparametric MRI after a negative biopsy, this will incur significant costs, which may not be offset by the reduced need for biopsies.

Implementation of the recommendations for advising men with a negative initial biopsy about their risk of prostate cancer would not have any important resource implications.

Barriers to implementation

At present, facilities for performing multiparametric MRI and expertise in its interpretation are limited to major metropolitan centres.

The cost of this imaging procedure may be a deterrent for some men. There is currently no Medicare Item number for multiparametric MRI in assessment of the prostate. However, the Prostate Cancer Foundation of Australia is collaborating with the Australian Government Department of Health, the Urological Society of Australia and New Zealand, and The Royal Australian and New Zealand College of Radiologists to establish item numbers for multiparametric MRI.

Footnotes

[i] Clinical questions were translated into the PICO framework: population, intervention (or exposure), comparator and outcome (see Appendix 3).

[ii] Measures of PSA kinetics include absolute increase in serum total PSA per year (PSA velocity) and time to doubling of serum total PSA (PSA doubling time). Both are used as indicators of increased risk of prostate cancer (see Testing with variants of PSA to improve sensitivity after an initial total PSA ≤ 3.0 ng/mL).

[iii] 'Atypical small acinar proliferation' and 'atypical glands suspicious for carcinoma' are synonymous classifications.[21][22] Accordingly, we have combined the evidence from published reported using either classification, although each was treated as a separate classification in the NICE systematic review.

[iv] Refer to Urological Society of Australasia position statement: Status of mp-MRI prostate 2012: report from the MRI Prostate Working Party (available at [1]]).

[v] See Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. European urology 2013; 64: 544-552.[23]

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Discussion

Supporting attachments

Foreword

As Patron of the Prostate Cancer Foundation of Australia I am well aware of the health risks posed by prostate cancer.

Ever year almost 20,000 Australian men are diagnosed with this disease and sadly 3,300 men die of it. This makes prostate cancer the second most common cause of male cancer deaths in Australia and the fourth most common cause of male deaths overall.

Prostate cancer can affect any man, changing their lives and touching the lives of their families.

Guidelines developed in partnership with

Prostate Cancer Foundation of Australia

Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

The purpose of these guidelines is to provide clear, consistent, evidence-based guidance on PSA testing and the early management of test-detected prostate cancer.

Published: 2015

National Health and Medical Research Council

I welcome the development of these guidelines and the contribution they will make to the health and well-being of men around the nation.

Governor-General of the Commonwealth of Australia,
His Excellency General the Honourable Sir Peter Cosgrove AK MC (Retd)

Guideline development process

Guidelines developed in partnership with

Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

Published: 2015

National Health and Medical Research Council

Introduction

Prostate Cancer Foundation of Australia (PCFA) initiated the process to develop a clinical practice guideline for PSA testing and management of test-detected prostate cancer. This guideline is a collaborative project between PCFA and Cancer Council Australia.

Development began in November 2012 after NHMRC agreed to consider approving the guideline, provided it were to be developed according to NHMRC procedures and requirements. To better describe the scope of the guideline, the title was changed to *Clinical practice guidelines for PSA testing and early management of test-detected prostate cancer*. Financial support for the guideline project was provided by PCFA with Cancer Council Australia contributing in kind resources of their guideline development team.

Contents

Guideline development group

Following a consultation process with key stakeholders involved in cancer control and clinical care delivery, including the Urological Society of Australia and New Zealand (USANZ) and the Royal College of Pathologists of Australasia (RCPA), PCFA invited a multidisciplinary group of relevant experts to develop a clinical guideline for PSA testing and clinical care immediately following test-detected prostate cancer. This was to ensure that representatives from all specialities and disciplines involved in the diagnosis and management of prostate cancer were represented. Two consumer representatives were also invited to be part of the Expert Advisory Panel (EAP) (see Appendix 2).

PCFA and Cancer Council Australia appointed a steering committee. The Project Steering Committee was responsible for the overall management and strategic leadership of the guideline development process. The Project Steering Committee ensured that all deliverables agreed in the project plan were delivered to acceptable standards in accordance with NHMRC requirements.

A project team based at Cancer Council Australia conducted the systematic reviews, comprising of systematic literature searches, literature screening against pre-determined inclusion and exclusion criteria and critical evaluation and data extraction of the included literature. The project team was responsible for liaising with the EAP members in regards to content development and content review and compiling the document.

The clinical practice guideline was developed according to the procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.[1] The development program was designed to meet the scientific rigour required by the standard for developing high quality, evidence-based clinical practice guidelines. A series of NHMRC resources and handbooks[2] [3] [4] [5] [6] [7] [8] [9] [10] guided the process and outlined the major steps and expectations involved in developing guidelines. These documents provided the definitions and protocols for developing research questions and search strategies, conducting systematic literature reviews, summarising and assessing the relevant literature and finally, formulating and grading the recommendations. They also included checklists and templates created to satisfy designated standards of quality and process.

At its initial meeting the Guidelines Expert Advisory Panel developed clinical questions. The questions were allocated to specific Guidelines Expert Advisory Panel members to act as lead authors according to their areas of expertise. Each lead author team was able to co-opt additional experts, who were not part of the Expert Advisory Panel, as co-authors for their allocated questions. These question-specific groups are referred to as Question Specific Working Parties in this guideline document. The Project Steering Committee assessed the suggestion of any additional co-authors including their declaration of interest (see Appendix 6).

Steps in preparing clinical practice guidelines to NHMRC criteria

For every question the below steps were followed:

1. Develop a structured clinical question (PICO question)

2. Search for existing relevant guidelines and systematic reviews

3. Process if relevant clinical practice guideline was identified or not

3a If no relevant clinical practice guideline was found	**3b If a relevant clinical practice guideline was found and assessed as suitable for adaption**
Check if an existing systematic review of high quality exists and can be used to inform the systematic review process	Conduct systematic literature review update for the question of the existing clinical practice guideline
Developing the systematic review protocol and systematic literature search strategy for each PICO question	Screening of literature update results against pre-defined inclusion and exclusion criteria

Conducting the systematic literature search according to protocol Screening of literature results against pre-defined inclusion and exclusion criteria Critical appraisal and data extraction of each included article	Critical appraisal and data extraction of each new included article Update evidence table of evidence review of existing guideline with new literature update results

4. Summarise the relevant data

5. Assess if meta-analysis should be undertaken

5a If meta-analysis is decided to be undertaken as part of the systematic review	**5b No meta-analysis**
Formulate rationale for meta-analysis Select studies for inclusion Extract data Perform statistical analysis Present results	Continue with step 6

6. Assess the body of evidence and formulate recommendations

7. Write the content narrative

Developing a structured clinical question

A wide range of questions was proposed for research. The questions focused on diagnosis, prognosis, risk and interventions. All proposed questions were reviewed on the basis of their purpose, scope and clinical importance to the target audience and were structured according to the PICO (populations, interventions, comparisons, outcomes) framework (see Appendix 3). The Question Specific Working Parties provided the systematic review team with feedback to refine the PICO questions.

Search for existing relevant guidelines and systematic reviews

For each PICO question, the National Guideline Clearinghouse the [www.cancerview.ca Guidelines Resource Centre] as well as the scoping search for the PICO question were scanned for relevant clinical practice guidelines that could potentially be suitable for adaption.

If an existing guideline was identified, the guideline was assessed for adaption according to the ADAPTE process. If suitable, the guideline systematic review was adapted as outlined in Guideline adaption for PICO questions 8.1, 8.2 and 9 (NICE).

Relevant guidelines that did not meet the criteria for adaption were checked for systematic reviews that could be used as a source of relevant references to inform the systematic review process for the PICO question. Full systematic reviews were then performed as outlined in the following sections.

Developing a systematic search strategy

For each PICO question, systematic literature search strategies were developed by the technical team.

Most searches were directed to prostate cancer as a generic base. Searches were limited or widened as necessary according to the PICO structure using keywords or MESH and subject terms. Systematic search strategies were derived from these terms for each included electronic databases. The included standard databases searched were Medline, Embase, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects and Health Technology Assessment for all questions. The psychosocial questions also included CINAHL and PsycINFO databases to retrieve relevant literature.

Conducting the systematic literature search according to protocol

Clinical practice guidelines should be based on systematic identification and synthesis of the best available scientific evidence.[2] For each clinical question, that required a systematic literature review, literature searches were conducted systematically with the literature cut-off date of 1 March 2014. The following electronic databases were part of the systematic literature search strategy:

- *Medline:* bibliographic references and abstracts to articles in a range of languages on topics such as clinical medical information and biomedicine, and including the allied health fields, biological and physical sciences
- *EMBASE:* major pharmacological and biomedical database indexing drug information from 4550 journals published in 70 countries
- *Database of Abstracts of Reviews of Effects and Health Technology Assessment*: contains details of systematic reviews that evaluate the effects of healthcare interventions and the delivery and organisation of health services
- *The Cochrane Database of Systematic Reviews*: contains systematic reviews of primary research in human health care and health policy, and are internationally recognised as the highest standard in evidence-based health care
- *CINAHL*: bibliographic references and abstracts to journal articles, book chapters, pamphlets, audiovisual materials, software, dissertations, critical paths, and research instruments on topics including nursing and allied health, biomedicine, consumer health, health sciences librarianship, behavioural sciences, management and education
- *Psychinfo*: bibliographic references and abstracts to journal articles, book chapters, dissertations and technical reports on psychology; social, clinical, cognitive and neuropsychology; psychiatry, sociology, anthropology and education, with source material from a wide range of languages.

A search filter to retrieve relevant literature considering Aboriginal and Torres Strait Islander peoples was added to each question.

Additional relevant papers from reference lists and, where appropriate, clinical trial registries, were also identified for retrieval as part of the snowballing process.

The full detailed systematic literature search strategy for every clinical question is fully documented in the technical report of the question (see Technical report.

Screening of literature results against pre-defined inclusion and exclusion criteria

Part of the systematic review process is to screen all retrieved literature results against the pre-defined inclusion and exclusion criteria in two stages.

a) First screen

During the first screening round, the titles and abstracts of all retrieved literature were screened by one or two reviewers. All irrelevant, incorrect and duplicates were removed.

b) Second screen

A second screen was undertaken based on the full article. Two reviewers assessed each article for inclusion against the pre-defined inclusion and exclusion criteria for each question. In the case of a disagreement between the reviewers, a third independent reviewer assessed the article against the inclusion and exclusion criteria. Articles that met the inclusion criteria were forwarded for quality assessment and data extraction.

Critical appraisal and data extraction of each included article

Two assessors independently assessed the risk of bias of each of the included studies using a study design specific assessment tool and where necessary pre-specified criteria (see Technical report) for all quality assessment tools). Any disagreements were adjudicated by a third reviewer.

For all included articles, the relevant data was extracted and summarised in study characteristics and evidence tables. Each data extraction was checked by a second assessor. These tables are included in the technical report for each question (see Technical report.)

Guideline adaption for PICO questions 8.1, 8.2 and 9 (NICE)

For clinical questions 8.1, 8.2, and 9 (NICE), the National Institute for Health and Care Excellence (NICE) guideline[11] for the management of prostate cancer was identified as potentially relevant and were assessed for potential adaption. The ADAPTE process[12] (particularly steps 2.2-2.5) was followed to establish if the guidelines were suitable for adaption.

To be considered for adaptation or adoption for this guideline, an existing guideline must:

- be assessed using the AGREE instrument for the domains rigour, clarity and editorial independence
- score at least 70% for each of these domains
- address PICO question(s) sufficiently similar to the PICO question(s) asked by the relevant working party (i.e. Do the recommendation(s) answer our question(s)?).

In the first instance, the NICE guidelines were assessed by four independent assessors using the three domains: rigour of development, clarity of presentation and editorial independence of the AGREE II instrument. The NICE guidelines scored 84.4% in the domain rigour of development, 76% in the domain clarity of presentation and 85.4% in the domain of editorial independence. The lead authors for PICO questions 8.1, 8.2 and 9 (NICE) were then approached by the systematic review team to verify that the PICO question addressed in the existing NICE guideline was suitable and relevant.

The systematic review team then updated the NICE systematic reviews to 1 March 2014 for the questions to be adapted. The literature was searched using the NICE literature search strategies and the results were screened against inclusion and exclusion derived from the NICE evidence review (see Screening of literature results against pre-defined inclusion and exclusion criteria). Included studies were assessed for quality and data extraction (see Critical appraisal and data extraction of each included article). The evidence tables from the NICE guidelines were updated with the study results from the updated literature review and included in the technical report for the relevant PICO question. The term “Updated Nice systematic review” is used in the narrative of these guideline questions to refer to the studies identified in the literature update of the NICE systematic review.

Meta-analysis for clinical question 7

For clinical question 7, a meta-analysis was conducted as part of the systematic review. The meta-analysis rationale was formulated. The relevant data was extracted from the studies included in the systematic review. The statistical analysis was conducted and the results presented. The analysis used logistic regression with generalised estimating equation adjustment to account for multiple (sometimes one but mostly two or more) biopsy components analysed from each man (using the patient identifier as the panel variable). The technical report for this question details the steps followed and includes the meta-analysis results.

Summary of the relevant data

For each outcome examined, the results, level of the evidence, the risk of bias due to study design, and the relevance of the evidence for each included study were documented a body of evidence table.

Each question was addressed by a systematic review resulting in a systematic review report. All systematic review reports are published in the technical report of the guidelines. Levels of evidence are shown below.

Table 1 . Designations of levels of evidence according to type of research question (NHMRC, 2009)

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening

I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study

III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Assess the body of evidence and formulate recommendations

The technical report for each question was forwarded to each question-specific author team. The author teams in collaboration with the systematic review team (who conducted the systematic reviews and provided the technical reports) assessed the body of evidence and completed the NHMRC Evidence Statement form to record the volume of the evidence, its consistency, clinical impact, generalisability and applicability and developed evidence statements (see Technical report.) The process is described in *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines (2009)*.[10]

Following grading of the body of evidence and development of evidence statements, expert authors were asked to formulate evidence-based recommendations that related to the summarised body of evidence. The method of grading recommendations is shown in Table 2.

Table 2: Grading of recommendations

Component of	**Recommendation Grade**

Recommendation	A Excellent	B Good	C Satisfactory	D Poor
Volume of evidence [1**]	one or more level I studies with a low risk of bias or several level II studies with a low risk of bias	one or two level II studies with a low risk of bias or a systematic review/several level III studies with a low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies /systematic reviews with a high risk of bias
Consistency [2**]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

[1] Level of evidence determined from level of evidence criteria

[2] If there is only one study, rank this component as 'not applicable'

[3] For example results in adults that are clinically sensible to apply children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

[**]For a recommendation to be graded A or B, the volume and consistency of evidence must also be graded either A or B!

Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

The overall recommendations grade are shown in table 3.

Table 3: Overall recommendation grades

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

In addition to developing evidence-based recommendations as a result of the systematic review for a question, expert authors could also draft consensus-based recommendations in the absence of evidence after having performed a systematic review or practice points, when a matter was outside the scope of the search strategy for the systematic review. The NHMRC approved recommendation types and definitions are shown in table 4.

Table 4: NHMRC approved recommendation types and definitions

Type of recommendation	Definition
Evidence-based recommendation	A recommendation formulated after a systematic review of the evidence, indicating supporting references
Consensus-based recommendation	A recommendation formulated in the absence of quality evidence, after a systematic review of the evidence was conducted and failed to identify admissible evidence on the clinical question
Practice point	A recommendation on a subject that is outside the scope of the search strategy for the systematic review, based on expert opinion and formulated by a consensus process

Source: National Health and Medical Research Council. Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council, 2011

Writing the content

For each question, the assigned lead authors were asked to draft their guideline chapter using the following format:

- general introduction to the clinical question
- background to the clinical question, including its clinical importance and historical evidence, where relevant
- review of the evidence, including the number, quality and findings of studies identified by the systematic review
- evidence summary in tabular form including evidence statements, levels of evidence of included studies, and reference citations
- evidence-based recommendation(s) and corresponding grade(s), consensus-based recommendations and practice points
- implications for implementation of the recommendations, including possible effects on usual care, organisation of care, and any resource implications
- discussion, including unresolved issues, relevant studies currently underway, and future research priorities
- references.

The content draft was then reviewed by all Question Specific Working Party members. The draft documents underwent several iterations until agreement between the members of the Question Specific Working Parties on these drafts was reached.

Review of the draft chapters

The complete draft guideline document with all draft chapters was circulated to the Guidelines Expert Advisory Panel. The whole group was asked to review the content and submit feedback. Members were asked to submit further suggestions on consensus-based recommendation and practice points.

A face-to-face meeting with all Expert Advisory Panel members was held to review and finalise the draft guidelines for public consultation. Prior to this meeting, the latest iteration draft guidelines were circulated. All panellists were asked to review the content, individual recommendations and practice points in detail, and to identify and note any controversies and points to be discussed at the group meeting. During the meeting, each recommendation and practice point was tabled as an agenda point. Each was reviewed and approved by consensus, which was reached by voting. The Expert Advisory Panel Chairperson nominated a particular recommendation/practice point to be reviewed and the panellists had the opportunity to discuss any issues and suggest revisions to recommendations and practice points. Each recommendation and practice point was approved once the eligible panellists (excluding representatives of the funding bodies and panellists who cannot vote due to conflict of interest) have reached consensus.

Public consultation

A complete draft of the guideline was sent out for public consultation from 4 December 2014 to 16 January 2015. The public consultation of the guideline was launched at the joint meeting day of the Union for International Cancer Control (UICC) World Cancer Congress and the Clinical Oncology Society of Australia (COSA) Annual Scientific meeting held on 4 December 2014 in Melbourne. The aim of this was to give the draft guidelines significant exposure to the international as well as the Australian cancer community. Submissions were invited from the general public and professional societies and groups and other relevant stakeholders. The consultation was publicised by advertisement in a national newspaper, and by contacting professional societies and groups, consumer groups and other relevant stakeholders.

All feedback on the draft received during the consultation period in Australia was compiled and sent to the relevant Question Specific Working Party to review their draft content, assessing and considering the submitted comments. Each additional submitted paper during public consultation was be assessed by the methodologist team against the systematic review protocol. Another face-to-face meeting was organised amongst the EAP to review all public consultation comments and the amended content. Subsequent changes to the draft were agreed by consensus, based on consideration of the evidence. The same consensus process that was followed during the face to face EAP meeting prior to public consultation was followed again. All changes resulting from the public consultation submission reviews were documented and made accessible once the guidelines are published.

A final independent review of experts in their fields was conducted before the final draft was submitted to NHMRC Council. Any further suggestions by the independent expert reviewers will be integrated in the final draft and then submitted to NHMRC Council for approval.

Organisations formally endorsing the guidelines

The following medical colleges and professional bodies were approached to endorse the guideline:

- Australian College of Rural and Remote Medicine (ACRRM)
- Medical Oncology Group of Australia Incorporated (MOGA)
- Royal College of Pathologists of Australia (RCPA)
- Royal Australian College of Physicians (RACP) - Adult Health Division
- Royal Australian College of Physicians - Australian Chapter of Palliative Medicine (AChPM, RACP)
- Royal Australian College of Physicians - Australian Faculty of Public Health Medicine (AFPHM, RACP)
- Royal Australian College of Surgeons (RACS)
- Royal Australian College of General Practitioners (RACGP)
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Urological Society of Australia and New Zealand (USANZ).

Formal endorsement of the guidelines was granted from:

- Australian College of Rural and Remote Medicine (ACRRM)
- Royal College of Pathologists of Australia (RCPA)
- Royal Australian College of General Practitioners (RACGP)

- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Urological Society of Australia and New Zealand (USANZ).

Dissemination and implementation

PCFA and Cancer Council Australia will take the lead in disseminating the guideline in Australia and are following a multi-strategy approach for the dissemination and implementation of the guideline, as this has shown to positively influence guideline uptake.[13] [14]

This will include a campaign to raise awareness of the new guidelines that incorporates organised media coverage through multiple outlets and an official launch at an international conference. The guideline will be distributed directly to relevant professional and other interested groups and through meetings, national and international conferences, and other professional development and continuing medical education (CME) events. A significant effort will be made to have the guideline introduced to senior undergraduate medical students and to encourage the relevant learned colleges to support the guideline and to foster their integration into hospital and community practice through resident and registrar education activities.

The guideline will be made available as a print publication, which can be ordered from PCFA and Cancer Council Australia. In addition, the guideline will also be made available as an online guideline via the Cancer Council Australia Cancer Guidelines Wiki. The online guideline version increases availability as well as accessibility, and usage will be tracked and analysed with a web analytics solution. Interlinking and listing the guidelines on national and international guideline portal is an important part of the digital dissemination strategy. Important Australian health websites, such as EviQ and healthdirect Australia will be approached to link to the online guideline. The guideline will also to be listed on national and international guideline portals such as Australia's Clinical Practice Guidelines Portal, Guidelines International Network guidelines library and National Guidelines Clearinghouse. The Cancer Guidelines Wiki is a responsive website that is optimised for mobile and desktop access. When accessing the guidelines with a mobile and tablet device, an icon can be easily added to the homescreen of mobile devices, offering easy mobile access.

In addition, the final guideline document will be launched via email alert to professional organisations, interested groups and clinical experts in the field, directing them via URL link to the online guideline and all associated resources. Future promotion will be conducted through print and social media campaigns as well as disseminating the guideline through further meetings, national and international conferences and other CME events. Local expert leaders will be identified and approached to facilitate dissemination and act as champions for the guidelines.

As part of the online guideline, online learning modules are planned to be developed to reinforce the guidelines content knowledge for participants, thus support guideline implementation and uptake. Programs will be developed using QStream (http://qstream.com/company/brain-science), a clinically proven online education method that was originally developed by Harvard Medical School. QStream programs have shown to improve knowledge acquisition in a number of randomised trials with medical practitioners.[15] [16] [17] [18][19] [20]

The Cancer Guidelines Wiki is based on semantic web technology, so the guidelines are available in a machine-readable format, which offers the possibility to easily integrate the guideline content with systems and web applications used in the Australian healthcare context.

Use of the guidelines as part of core curriculum in specialty exams will be encouraged. It is recognised that a planned approach is necessary to overcome specific barriers to implementation in particular settings and to identify appropriate incentives to encourage uptake of guideline recommendations. Implementation of the guidelines will require a combination of effective strategies and may include further CME initiatives and interactive learning, the development and promotion of computer-assisted decision aids and electronic decision-support systems, and the creation of audit and other clinical tools.

To support the implementation of this guideline a decision aid for men considering having a PSA test, and men who have had a positive PSA test result and are considering watchful waiting or active surveillance instead of immediate treatment are going to be developed.

Future updates

The incoming literature updates will continue to be monitored for each systematic review question. If there is strong evidence emerging in a specific area of PSA testing, the Expert Advisory Panel will be reconvened to assess if this warrants a guideline update (full or partly). It is recommended that these guidelines be updated after 3 years.

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Introduction

Guidelines developed in partnership with

Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

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Contents

About this guideline

For information about this guideline, see here.

Prostate cancer in Australia

Prostate cancer is an important public health issue. It is the second most commonly diagnosed cancer in Australian men after non-melanoma skin cancer. Over the most recent decade of reports on cancer incidence in Australia, prostate cancer diagnoses increased, from 11,477 in 2000 to 19,993 in 2011.[1] In 2011, men were estimated to have a one in seven chance of being diagnosed with prostate cancer by age 75 and a one in five change of being diagnosed by age 85. With the growing Australian population, increasing life expectancy and the expectation of continuing increases in prostate cancer incidence (due mainly to increasing age), the Australian Institute of Health and Welfare has estimated that the number of prostate cancers diagnosed in Australia in 2020 will lie between 25,000 and 31,000.[2]

The latest figures from the Australian Institute of Health and Welfare show that 3,079 men died from prostate cancer in 2012.[3] That number represents 4.1% of all deaths in men and 12.6% of all cancer deaths in men, making prostate cancer second only to lung cancer as the most common cause of cancer death in men. Illness and disability associated with prostate cancer also has a large impact on Australian men's lives. Based on 2010 data, it was estimated that 42,500 disability-adjusted life years (DALYs) were lost to prostate cancer – second only to lung cancer (56,800 DALYs).[4]

Men at risk of dying from prostate cancer

The main objective of early diagnosis of prostate cancer is to reduce the rate of death from prostate cancer. Each year, on average, eight Australian men younger than 50 years of age die from prostate cancer (estimated from the annual average over the years 2002 to 2011[3]). From a rate of about one death per year per 100,000 men aged 45–49 years, mortality in Australia increases two- to four-fold with each 5-year increase in age, to a maximum of about 800 deaths per year per 100,000 men aged 85 years and over.[3]

Rates of death due to prostate cancer are highest in countries with predominantly European origin populations; the lowest rates are observed in Middle Eastern and Asian populations.[5] While available data are limited, mortality rates also appear to be high in African countries, and African American men are at high risk of death from prostate cancer.[5][6]

Within Australia, mortality rates from prostate cancer are highest among men born in Australia, New Zealand, and Western, Northern and Southern Europe, and materially less in men born in Eastern Europe, the Middle East and Asia, consistent with the international patterns.[7] In addition, mortality rates are highest among men of lowest socioeconomic status, and become progressively higher with increasing remoteness of a man's place of residence.[7]

Available evidence indicates that the rate of mortality from prostate cancer among Australian Aboriginal men is higher than in other Australian men but that incidence is lower.[8] This disparity suggests that diagnosis of prostate cancer is later or its treatment poorer in Aboriginal men. Recent research suggests the latter is the case.[9]

A family history of prostate cancer, especially having a male first-degree relative diagnosed with prostate cancer before age 65 years,[10] increases a man's risk of developing it. The mutations best known to increase risk for prostate cancer are the BRCA1 and BRCA2 gene mutations, which are associated with a high risk of breast cancer, and the HOXB13 mutation. Other gene mutations that increase risk to a small or moderate degree are regularly reported. Various lifestyle factors have been reported as associated with prostate cancer risk, but only one – overweight and obesity (which may be associated with advanced prostate cancer only) – appears to be established with sufficient certainty to be a target for risk reduction.[11]

Testing for the early diagnosis of prostate cancer

Efficacy of testing

This guideline informs testing for the early diagnosis of prostate cancer in men in whom prostate cancer is likely to occur and can be detected, and who do not currently have any symptoms that suggest they might have prostate cancer. Although testing in this context is commonly referred to as 'screening', we will avoid this term here. We do so to prevent confusion between testing offered in an organised way to a specified target group of men at risk of prostate cancer in the population (screening), and testing considered during men's usual interactions with the health system, which is the context of this guideline.

A test for early diagnosis of cancer is a test that aims to detect a cancer before it causes symptoms and thus, through early treatment, to increase the likelihood that the cancer will be cured. There is currently no test that can accurately identify men who have prostate cancer among men who have no symptoms that suggest prostate cancer. To be considered accurate, a test for early diagnosis of prostate cancer would have to be highly sensitive and highly specific: that is, to be highly likely to be 'positive' when prostate cancer is present and highly likely to be 'negative' when it is not. The two tests that are commonly used to detect prostate cancers early are measurement of PSA in blood and digital rectal examination (DRE), in which a doctor examines the prostate by feeling it through the rectum. Both tests can identify men who may have prostate cancer, but they are not very accurate in doing so.

While the PSA test may not be accurate in detecting prostate cancer early, it may be accurate enough to be considered efficacious in reducing risk of death from prostate cancer, which is the main aim of early diagnosis. Australia's National Health and Medical Research Council (NHMRC) recently commissioned a systematic review of evidence on the efficacy of PSA testing in reducing rates of mortality and morbidity due to prostate cancer in asymptomatic men. The NHMRC review's conclusions included the following:[12]

> *In asymptomatic men:*
>
> - *The present evidence is inconsistent as to whether there is an effect of PSA testing, with or without DRE, on the risk of prostate cancer-specific mortality compared with no PSA testing, although the possibilities of no effect or a small protective effect cannot be excluded;*
> - *PSA testing with or without DRE reduces the risk of prostate cancer metastases at diagnosis compared with no PSA testing; and*
> - *It is unknown if PSA testing, with or without DRE affects quality of life due to advanced prostate cancer, compared with no PSA testing.*

Inconsistency in the findings of the randomised controlled trials of PSA testing, with or without DRE, underlies NHMRC's equivocal finding on the evidence that PSA testing reduces death from prostate cancer. The US Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial[13] found a statistically non-significant 13% **increase** in prostate cancer-specific mortality after 13 years of follow-up in men 55–74 years of age offered annual PSA testing for 6 years and annual DRE for 4 years; the European Randomized Study of Screening for Prostate Cancer (ERSPC)[14] found a statistically significant 21% **fall** in prostate cancer-specific mortality after 11 years of follow-up in men aged 55–69 years offered PSA testing every two-to-four years, generally without DRE. Three other earlier and smaller randomised or pseudo-randomised trials obtained results similar to those of the PLCO.[15]

The pooled results of PLCO and the three earlier and smaller trials are statistically incompatible with those of the ERSPC, which is, in reality, a result of pooling the results of seven smaller, nationally defined trials working in cooperation but to somewhat different protocols. There is no way of resolving the inconsistency among these trials and reaching an evidence-based conclusion as to whether or not PSA testing is efficacious in reducing mortality from prostate cancer.

While the prevention of deaths due to cancer is the main goal of testing in asymptomatic men, there are other potential benefits. These include reduction in diagnosis of cancer when it is already advanced, a reduction in the suffering that can precede death from advanced cancer, and a reduction in adverse effects of therapy used to control advancing cancer. Available evidence indicates that PSA testing reduces the risk of diagnosis of prostate cancer with metastases already present, but is largely silent as to whether PSA testing can prevent reduction in quality of life due to advanced cancer.[12]

Rates of PSA-based testing in Australia

Analysis of Medicare Australia's Medical Benefits Schedule (MBS) records shows that 778,469 PSA tests were recorded as Medicare item number 66655 in 2012.[16] This number underestimates the actual number of PSA tests done, perhaps by as much as 40%.[17] It suggests that each year at least 20% of men aged between 45 and 74 years have a PSA test, presumably for the purpose of early diagnosis of prostate cancer. By way of comparison, the latest figures from the Australian Institute of Health and Welfare show that the participation rate of eligible women (those aged 50–69 years) in the BreastScreen Australia program for 1997–1998 was 54.3%, which, being a program of biennial screening, averages at about 27% per year.[18]

A 2012 survey of 1,431 men suggests that GPs are the key influencers of testing either by suggesting that men have a PSA test as part of a routine check-up or by requesting a PSA test without consulting the men about it.[19]

There is evidence that many men are undergoing PSA testing with inappropriate frequency and that men in certain groups who should be excluded from testing on the basis of previous PSA test results, medical co-morbidity or limited life expectancy, are still being tested.[20][21][22]

Harms associated with PSA testing

The outcome of prostate cancer is strongly related to the stage and grade of the disease at diagnosis. PSA testing can detect cancers at a clinically localised stage, and at a lower grade than prostate cancers detected in other ways. This fact underlies the likely ability of PSA testing of asymptomatic men to reduce mortality from prostate cancer, as suggested by the results of the ERSPC[23] and the Gøteborg prostate cancer screening trial.[24]

It also underlies the likelihood that a proportion of prostate cancers detected as a result of positive PSA tests would never have bothered the men in which they were detected, had these men not been tested. Such cancers are commonly referred to as 'over-diagnosed' cancers. They have been estimated to account for as many as 20–40% of cancers diagnosed following a positive PSA test.[25] There is currently no known way of distinguishing over-diagnosed cancers from cancers that would have gone on to cause symptoms and possibly death; thus, prostate cancers detected through PSA testing have to be treated with the same seriousness as any cancer of their stage and grade. Hence a positive PSA test can lead to a cascade of further investigation and treatment that may cause harm to men, some of whom would not otherwise have been diagnosed with prostate cancer and would not benefit from treatment.

The only harms PSA testing may cause directly are the anxiety and distress that a positive test engenders whether a cancer is subsequently diagnosed or not. Indirect harms include those associated with biopsy performed as a result of PSA testing – inconvenience, discomfort, and occasional, but potentially serious, adverse health effects (e.g. bleeding or infection) – especially when the test was a false positive test (i.e. no prostate cancer was found subsequently by biopsy) or the cancer found was an over-diagnosed cancer.

Treatment of a prostate cancer found following a positive test can be a cause of distress, discomfort and, quite frequently, adverse effects. The major adverse effects consequent on prostate cancer treatment are:[26]

- urinary incontinence, which is common soon after treatment and persists in some 12–15% of men treated by radical prostatectomy, and other urinary problems in men treated by radiotherapy
- erectile dysfunction in men treated by radical prostatectomy, radiotherapy or androgen deprivation therapy, which is common soon after treatment and persists in some 70% of men, although probably not attributable to the therapy in all cases
- bowel problems, which are most common after external beam radiotherapy and affect some 20% of men.

These harms are usually offset by the cure or amelioration of the disease that treatment can bring. However, men with over-diagnosed cancer will experience harm without compensating benefit.

Balance of benefits and harms

A test for early detection is often evaluated on the basis of whether the benefits exceed the harms. Indeed, Australia's framework for population-based screening includes as an absolute requirement that screening programs offer more benefit than harm to the target population.[27] Uncertainty about the efficacy of PSA testing in reducing prostate cancer mortality, and about the extent of over-diagnosis, make any estimate of the balance of benefits and harms from PSA testing very uncertain. On this basis many reviews do not recommend PSA testing.

Two published estimates based on well-regarded statistical models of PSA testing, which assume the ERSPC's estimate of the reduction in prostate cancer mortality due to testing, have reached different conclusions. Using the Dutch MISCAN model, Heijnsdijk et al (2012)[28] estimated that men who had annual PSA testing from age 55 to 69 years gained, on average, 0.056 quality-adjusted life years (QALYS) as a result of testing; that is, on average the benefits exceeded the harms. Using the Fred Hutchinson Cancer Research Centre model, Pataky et al (2014)[29] estimated an average loss of 0.0004 to 0.0105 QALYs per man tested depending on the testing protocol; that is, on average, the harms exceeded the benefits. The difference in these conclusions appears to have been due mainly to differences between the two studies in the quality adjustments made to years of life lived in particular health states.

From these estimates, therefore, it is uncertain, at best, whether the benefits of PSA testing, measured in terms of quality life gained, exceed its harms. This reality underlies the decision, taken *a priori*, not to make a recommendation regarding population screening for prostate cancer in these guidelines. This position is consistent with the Australian Government's position. The 2014 update of the joint position statement *Prostate cancer screening in Australia*[30] by the Australian Health Ministers' Advisory Council and Cancer Council Australia concludes: 'An assessment of current evidence against the Population Based Screening Framework criteria indicates that the PSA test is not suitable for population screening, as the harms outweigh the benefits'. It is also consistent with recent international guidelines developed by the US Preventative Services Task Force [31] and Canadian Task Force on Preventative Health Care[32].

This position, however, does not exclude PSA testing as an informed choice taken by men in consultation with their doctors. The Australian Health Ministers' Advisory Council and Cancer Council Australia joint position statement on prostate cancer screening[30] also concludes that '…men considering being tested for prostate cancer should do so with information on both the benefits and harms of testing and treatment. We encourage men to speak to their doctor so they can make an informed choice about prostate cancer testing.' The Australian Government also facilitates PSA testing through the Medicare Australia Medical Benefits Schedule, Item 66655 of which allows payment of a benefit for PSA quantitation once in a 12-month period.[16]

The need for a PSA testing guideline

Given the large number of men in Australia who are tested annually, it is important to determine how to maximise the benefits, if there are benefits, and minimise the harms from PSA testing. In Australia there is now no commonly accepted guidance that applies to men who have decided to undergo PSA testing, indicating the optimal age to start testing and the frequency of testing. Nor is there specific guidance for men in high-risk groups, particularly men with a family history of prostate cancer. Further, there is no commonly accepted guidance on what represents a positive test result and the actions that should follow from such a result. Importantly, there is indirect evidence from substantial variation in the frequency of prostate biopsy relative to PSA testing among Australian States and Territories that decisions about what represents a positive test result are highly variable.[33]

Given this evidence, the current situation is far from ideal:

- Each year, according to figures derived from Medicare Benefits Schedule data, approximately 20% or more of men aged 45–74 years are tested for prostate cancer, presumably with the intent of early diagnosis.[33]
- Many men are undergoing PSA testing with inappropriate frequency, and many men are being tested who are not suitable for testing, on the basis of medical co-morbidity and/or limited life expectancy.[20][21][22]
- It is doubtful whether all, or even many, of the men who are tested have been given the opportunity for fully informed choice about whether or not to have a PSA test.
- Guidance given to men about PSA testing is inconsistent and often confusing.
- There is no consistent approach to determining the PSA concentration threshold that should prompt further investigation.
- There is no clear guidance on testing for men in known high-risk groups, such as men with a family history of prostate cancer.
- Some three to seven men must be diagnosed with and treated for prostate cancer to prevent one death from prostate cancer (assuming that the ERSPC results correctly characterise the efficacy of PSA testing in preventing prostate cancer death). These men diagnosed include an estimated 20–40% who, if they had not had a PSA test, would never have been bothered by their prostate cancer.
- The quality of the guidance given to men about their treatment options when diagnosed with prostate cancer is uncertain. There may also be insufficient consideration of active surveillance as a management option. Active surveillance involves a program of ongoing PSA testing and other testing of men with early-stage, low-grade cancer, in which radical treatment is offered only if the cancer shows signs of progressing or the man requests it.
- Men’s needs for support in managing adverse effects of treatment and their emotional response to the disease are often unmet.

As a result, there is a need for evidence-based clinical recommendations for prostate cancer testing that extend from informed decision-making about whether to be tested, through to decision-making and actions following a positive test result. In addressing this need, our overriding consideration was achieving the best balance between the benefits and harms of testing for early diagnosis of prostate cancer or, at the very least, minimising the harms consequent on testing. We hope that implementation of these recommendations will help achieve this balance for Australian men.

Basis for making recommendations on testing protocols

Given the context of this guideline, which is to advise men who decide to have a PSA test after they have been informed of the benefits and harms of testing, the Expert Advisory Panel decided to base its recommendations for testing protocols on the results of ERSPC; its various sub-studies; and epidemiological modelling based on the ERSPC data. To do otherwise would have prevented the Expert Advisory Panel from producing any guidance because, absent ERSPC finding, there would be no evidence on what testing protocol might be efficacious in reducing prostate cancer mortality. Should further research find that the ERSPC results are more unreliable than we have judged them to be, we would have to reconsider this decision and this guideline.

We considered it appropriate to base our recommendations on the ERSPC data for the following main reasons:

1. The pattern of evolution of the difference in cumulative prostate cancer mortality between ERSPC intervention arm and control arm men is exactly that expected if PSA testing were efficacious in reducing prostate cancer mortality: there was little difference between them up to about 7 years from study entry, thereafter cumulative mortality has diverged progressively with the better outcome in men offered PSA testing.[14]

2. There is a high degree of internal consistency in the ERSPC findings that adds to strength to the evidence it provides. While there was appreciable heterogeneity in the way the ERSPC was conducted in its seven component national centres, the relative risk (RR) of prostate cancer death in the intervention arm relative to the control arm in six of the seven centres was consistent with protection against prostate cancer death, ranging between 0.56 and 0.89.[14] The lowest RR (0.56) was in the Swedish (Gøteborg) centre, which offered testing every 2 years, not every 4 years as in the other centres; and the one outlier, an RR of 2.15, came from the small Spanish centre that, at the time of the analysis, had observed two deaths in the intervention arm and one in the control arm.[14]

3. There are two aspects of study conduct that would cause PLCO to underestimate efficacy of PSA testing.[34] Of all men randomised by PLCO, 45% had a PSA test in the 3 years before study entry, and an estimated 52% of men in the control arm had one in the period of the last intervention arm PSA test.[35] By way of comparison, an estimated 30.7% of the ERSPC control group was tested once or more during the study.[36] Further, 40.1% of PLCO intervention group men with a positive PSA test had a prostate biopsy within 1 year and 64% within 3 years of the test,[37] while in ERSPC biopsy compliance was approximately 90%.[38]

The ERSPC has recently published results from 13 years of follow-up.[23] While the estimated relative cumulative benefit at 13 years remains the same is it was at 11 years (an estimated 21% reduction in risk of prostate cancer death due to PSA testing), the absolute effect has increased from 0.46 prostate cancer deaths prevented per 1000 men randomised to PSA testing after 9 years of follow up, to 1.02 prevented per 1000 men after 11 years and to 1.28 per 1000 men after 13 years of follow-up.[23] In parallel, the estimated number of

cancers needed to diagnose to prevent one prostate cancer death fell from 48 at 9 years of follow-up to 35 at 11 years, and 27[i] at up to 13 years' follow-up.[23] These are trends that would be expected from introduction of an effective cancer screening test; the extra cancers diagnosed begin on day one, but the benefits in terms of deaths prevented are not seen for a number years (some 6–7 years in the case of prostate cancer). Thereafter, the deaths prevented continue to accumulate while testing continues, and for a period after it is discontinued.[39][40]

Purpose of this guideline

This guideline provides evidence-based recommendations for PSA testing and immediately consequent clinical care in Australia. Its main purpose is to provide guidance on:

- which testing protocol to recommend to men who decide in favour of testing, depending on their age and underlying risk of prostate cancer
- further investigation of an abnormal PSA test and the early management of prostate cancer diagnosed following such investigation.

The aim of the recommendations, through their application in practice, is to maximise the benefits and minimise the harms of PSA testing in men without symptoms suggestive of prostate cancer.

Intended users of this guideline

The target users of the guideline are:

- health professionals in primary care, such as general practitioners, advising men who are considering testing or have decided to be tested
- urologists and other health practitioners advising men who have had a positive PSA test, have had a prostate biopsy (either positive or negative for prostate cancer), or have been diagnosed with prostate cancer and are considering their management options.

The guideline will also be relevant to all other health service personnel involved in PSA testing and the diagnosis and management of prostate cancer, and to people involved in communicating risk, policy makers, and hospital and health service resource managers.

Target population

The clinical populations covered by the recommendations in this guideline are:

- asymptomatic men who on the basis of general knowledge ask their doctor about a PSA test
- asymptomatic men who have been told about the test by their doctor and are considering having one
- asymptomatic men without known prostate cancer who have decided to undergo PSA testing, after the benefits and risks have been explained to them
- men with early prostate cancer diagnosed after PSA testing.

Healthcare setting to which this guideline applies

This guideline provides recommendations for the care of men using Australian health services, specifically:

- primary care, including general practice and Aboriginal medical services
- urology services
- public and private hospitals.

Scope of this guideline

The guideline addresses the following areas:

- the increased risk of prostate cancer experienced by men who have a family history of prostate cancer
- PSA testing (decision support for men considering a PSA test, PSA testing strategies, the role of digital rectal examination, PSA testing and life expectancy, and the contribution of PSA variants to PSA testing)
- the increase in risk above average risk that would justify a change in PSA testing strategy, particularly the risk associated with a family history of prostate cancer
- investigations (indications for further investigations, prostate biopsy quality criteria, and follow-up to negative prostate biopsy)
- management (options for men with biopsy-diagnosed prostate cancer, the roles of active surveillance and watchful waiting, and protocols for implementing these management options)
- sociocultural aspects of PSA testing (whether special considerations apply to Aboriginal and Torres Strait Islander men, and whether socioeconomic factors affect testing).

A full list of all clinical questions that form the basis of this guideline is available in Appendix 3.

Methods used to develop this guideline

The guideline was developed in accordance with the 2011 NHMRC standard (*Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines*).[41]

Literature searches were conducted for each clinical question to identify evidence relevant to pre-specified populations, interventions (or exposure, for question 1), comparators and outcomes. Outcomes were selected for clinical relevance and included biopsy-diagnosed prostate cancer, metastatic prostate cancer, and death due to prostate cancer, depending on the clinical question. The evidence for all clinical questions was filtered to identify any findings specific to Aboriginal and Torres Strait Islander men. A detailed description of the guideline development process and methodology is given in Appendix 1 Guideline development process.

An Expert Advisory Panel comprised of representatives from all specialities involved in the diagnosis and management of men affected by prostate cancer, other scientists and consumer representatives was convened to develop the PSA testing recommendations in this guideline. The list of all Expert Advisory Panel members is available in Appendix 2 Committee members and contributors and the statement of competing interests is available in Appendix 6 Conflict of interest register. Details in regards to the funding, dissemination and recommended future updates of the guidelines are described in Appendix 1 Guideline development process.

Implementation

Cancer Council Australia and Prostate Cancer Foundation of Australia have initiated programs of work to develop tools to help men make informed choices about PSA testing, and to estimate life expectancy. When completed, these tools will be made available to health professionals.

In addition, both organisations plan to produce and publish a digest of the guideline that is easy for the average man to read and understand, and summaries of the guideline that are easy for health professionals to use in their day-to-day care for men's health.

Further, they will work together with other interested parties in developing and seeking implementation of health service, both clinical and non-clinical, policies and procedures that will facilitate use of the guideline's recommendations in practice.

Life of this guideline

It is inevitable that parts of this guideline will quickly become out of date as knowledge advances. Newly published literature relevant to each systematic review question will be monitored. If strong evidence supporting a change in the guideline accumulates, the Expert Advisory Panel will reconvene to assess if a guideline update is warranted. The guideline as a whole will be reviewed every three years and a decision made as to whether partial or full updating is required.

Footnotes

[i] The number needed to diagnose (NND) value of 17 in the latest ERSPC analysis may appear to be at variance with model-based NND estimates of 3 to 7.[13][28][29] It differs from the these estimates, however, in being based on only 13 years of follow-up from the beginning of screening, whereas the model estimates assume that members of the modelled cohort are followed until their death or attainment of a great age.

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List of clinical questions

Appendix 3 List of clinical questions

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Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

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Question No.	Clinical Questions	Corresponding PICO Question(s)
Risk		
1	What risk factors can identify Australian men who are at high risk of prostate cancer or death from prostate cancer? Suggested risk factors include: Family history	**1:** For Australian men, has a family history of prostate cancer been shown to be reliably associated with a 2.0-fold or greater increase in risk of occurrence of or death from prostate cancer when compared to men who do not have a family history of prostate cancer?
Testing		
2	What methods of decision support for men about PSA testing increase men's capacity to make an informed decision for or against testing?	**2:** In men without evidence of prostate cancer does a decision support intervention or decision aid compared with usual care improve knowledge, decisional satisfaction, decision-related distress and decisional uncertainty about PSA testing for early detection of prostate cancer?

Question No.	Clinical Questions	Corresponding PICO Question(s)
3	In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?	**3.1:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality or the incidence of metastases at diagnosis and offer the best balance of benefits to harms of testing? **3.2:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what PSA testing strategies with or without DRE perform best in detecting any prostate cancer or high grade prostate cancer diagnosed in biopsy tissue? **3.3:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer does a PSA level measured at a particular age in men assist with determining the recommended interval to the next PSA test?
4	How best can DRE be used, if at all, in association with PSA testing?	**4:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what is the incremental value of performing a digital rectal examination (DRE) in addition to PSA testing in detecting any prostate cancer?
5	What age or health status criteria should be used to identify men who would be unlikely to live long enough to benefit from PSA testing and who, in consequence, would not be offered PSA testing?	**5:** For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, how many years after the start of PSA testing is the benefit of PSA testing apparent?
		Free-to-total PSA % **6.1a:** For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring free-to-total PSA percentage improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with

Question No.	Clinical Questions	Corresponding PICO Question(s)
6	In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what tests for prostate cancer should be offered in addition to a PSA test? Candidate tests include: free-to total PSA % PSA velocity Prostate health index Repeated total PSA	a single total PSA result above 3.0 ng/mL? **6.1b:** For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring free-to-total PSA percentage improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL? **PSA velocity** **6.2a:** For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring PSA velocity improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL? **6.2b:** For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring PSA velocity improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL? **Prostate Health Index (PHI)** **6.3a:** For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring the Prostate Health Index (PHI) improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result above 3.0 ng/mL? **6.3b:** For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring the Prostate Health Index (PHI) improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a

Question No.	Clinical Questions	Corresponding PICO Question(s)
		single elevated total PSA result above 3.0 ng /mL? **Repeated total PSA** **6.4:** For asymptomatic men with initial total PSA above 3.0 ng/mL, does repeating the total PSA test and using an initial and repeat total PSA above 3.0 ng/mL as the indication for biopsy, improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL as the indication for biopsy?
Prostate biopsy and multiparametric MRI		
7	What constitutes an adequate prostate biopsy?	**7:** For men undergoing an initial prostate biopsy how many biopsy cores, which pattern of biopsy sampling sites and which approach constitute an adequate prostate biopsy?
8	If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?	**8.1:** In men who have been referred with suspected prostate cancer, what are the prognostic factors that determine the need for further investigation following a prior negative biopsy? **8.2:** In men with suspected prostate cancer whose initial TRUS biopsy is negative, what should be the next investigation(s)?
Active surveillance		
9	What should be the criteria for choosing active surveillance in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?	**9:** For men with biopsy-diagnosed 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 definitive treatment?
		10: For men with biopsy-diagnosed prostate cancer following an active surveillance

Question No.	Clinical Questions	Corresponding PICO Question(s)
10	What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?	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?
Watchful waiting		
11	What should be the criteria for choosing watchful waiting in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?	**11:** For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does watchful waiting achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment?
10	What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?	**10:** For men with biopsy-diagnosed 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?
12	What is the best monitoring protocol for watchful waiting and what should be the criteria for intervention?	**12:** For men with biopsy-diagnosed prostate cancer following a watchful waiting 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?

PSA testing and life expectancy

For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, how many years after the start of PSA testing is the benefit of PSA testing apparent? **(PICO[i] question 5)**

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Contents

Background

There is an inevitable delay between application of a test to detect cancer early and any reduction in cancer mortality a person or group of people may experience as result of the test. Therefore, testing people with only a short life expectancy may offer no benefit against which to balance the cost or inconvenience of the test or any short-term harm that may flow from it (e.g. consequences of a false positive test, or unnecessary treatment for a cancer detected that would never have manifest clinically during the person's lifetime).

Evidence

Time period for the benefit of PSA testing to become apparent

The ERSPC[1] and data from two of its component study centres (Rotterdam[2] and Gøteborg[3]) provided evidence on the time from first having a PSA test to the first appearance of a mortality reduction consequent on testing. This evidence was judged to be at moderate risk of bias. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

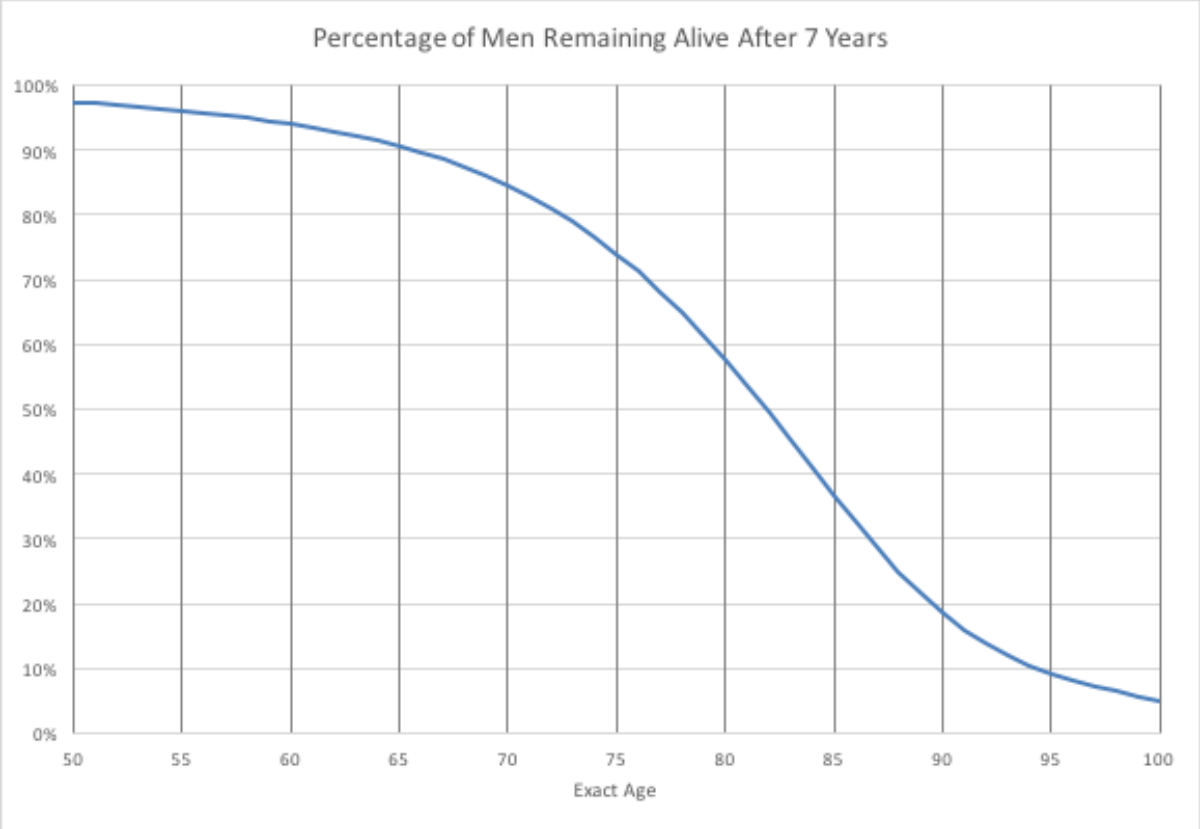
The ERSPC found little evidence that PSA testing at 2 or 4 yearly intervals reduced mortality before 7 years after testing began (RR 0.92; 95% CI 0.73–1.18). Thereafter, there was evidence of reduction in mortality at 8–9 years after testing began (RR 0.74; 95% CI 0.55–0.99), which was stronger again at 10–11 years after testing began (RR 0.62; 0.45–0.85).[1] The ERSPC and its Rotterdam and Gøteborg components also published plots of cumulative hazard of death from prostate cancer in screening and control arms by time since screening began (Nelson–Aalen method). Reading from these plots, it was estimated that divergence of the cumulative hazards was first evident at 7 years in ERSPC men aged 55–69 years, Gøteborg men aged 50–69 years and Rotterdam men aged 55–74 years, and at 6 years in Rotterdam men aged 55–69 years.

Evidence from the Gøteborg centre, with wider confidence intervals and higher risk of bias, suggests that the lower mortality from prostate cancer in the intervention group was no longer evident 9–12 years after testing ended.[4]

Likelihood that a man will survive long enough to benefit from PSA testing

The likelihood that an Australian of a given age will live for a certain number of years can readily be determined from the Australian Life Tables published by the Australian Government Actuary[ii]. For example, the percentage of men of a given age who will live for another 7 years, calculated from the Australian Life Tables 2010-12 – Males,56 is as shown in Figure 2.3. Reading from this Figure, for example, 50% of men aged about 83 years can be expected to live more than another seven years.

Figure 2.3. Percentage of Australian men of a given age remaining alive after 7 years from ages 50 to 100



Source: Australian Life Tables 2010-12 – Males[5]

The Australian Life Tables 2010-12 are based on Census data and therefore represent the mortality of men and women in average health for their age. Many older men and women have a number of co-morbidities, which can have a significant impact on life expectancy. Hence, ideally the mortality data would be stratified by health status to enable more accurate advice to be given to a man about whether he is likely to live long enough to benefit from PSA testing. That is beyond the scope of this guideline. However, development of an online calculator tool based on Australian data, and which does take account of health status, is underway.

Evidence summary and recommendations

Evidence summary	Level	References
For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, a reduction in the risk of death from prostate cancer was apparent	II	[4], [1], [2], [3]

Evidence summary	Level	References
at 6–7 years after the start of PSA testing.		

Evidence-based recommendation[?]	Grade
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.	**C**

Practice point[?]

When discussing the benefits and harms of PSA testing with older men or those with a potentially fatal chronic illness, explain each of the following:

- Testing can only be expected to prevent prostate cancer death that would have occurred more than 7 years in the future.
- If prostate cancer is diagnosed after the test, medium- to long-term quality of life may be better due to diagnosis and treatment of a cancer that could have become advanced in less than 7 years.
- If prostate cancer is diagnosed after the test, quality of life in the immediate short term may be poorer due to the harmful effects of treatment.

Practice point[?]

The percentage of men of a given age, and average health status for their age who are expected to live for another 7 years is as shown in the **table below**.

Age	Percentage of men remaining alive after 7 years
50	97%
55	96%
60	94%

65	91%
70	85%
75	74%
80	57%
85	37%
90	19%

Health system implications of these recommendations

Clinical practice

Implementation of the recommendation would require clinicians to consider life expectancy whenever they offer a PSA test. Current Australian guidelines for disease prevention in primary care advise that men with a life expectancy of less than 10 years are at reduced risk of dying from prostate cancer.[6] Reducing the estimate of the life expectancy at which a PSA test may have benefit from 10 years to 7 years may increase the number of men tested. However, it is not possible to predict whether there would be a net increase, reduction or no change in the number of men tested, because it not known whether all clinicians routinely discuss life expectancy when providing information about the risks and potential benefits of PSA testing, or the accuracy of life expectancy estimates in practice.

Resourcing

Implementation of this recommendation would have no significant resource implications.

Barriers to implementation

No barriers to the implementation of this recommendation are foreseen.

Footnote

[i] Clinical questions were translated into the PICO framework: population, intervention (or exposure), comparator and outcome (see Appendix 3).

[ii] The latest tables, the Australian Life Tables 2010-12, are based on the mortality of male and female Australians over the three calendar years centred on the 2011 Census of Population and Housing.[5]

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Discussion

PSA Testing strategies

Guidelines developed in partnership with

For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer:

- ***what PSA testing strategies (with or without DRE), compared with no PSA testing or other PSA testing strategies, reduce prostate cancer specific mortality or the incidence of metastases at diagnosis and offer the best balance of benefits to harms of testing?*** **(PICO[i] question 3.1)**
- ***what PSA testing strategies with or without DRE perform best in detecting any prostate cancer or high grade prostate cancer diagnosed in biopsy tissue?*** **(PICO[i] question 3.2)**
- ***does a PSA level measured at a particular age in men assist with determining the recommended interval to the next PSA test?*** **(PICO[i] question 3.3)**

Prostate Cancer Foundation of Australia

Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

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Contents

Background

Measurement of blood concentration of PSA is a test that can identify men who have an increased probability of having an undiagnosed prostate cancer and, as a result, may identify cancers at a stage at which they are more likely to be curable than if they presented clinically. However, tests aimed at diagnosing cancer early are never perfect. Some fraction of tests done will produce false positive results, prompting diagnostic tests, usually invasive, that do not find cancer to be present. Some, perhaps most, tests for early cancer also bring to light some cancers that would otherwise never have become clinically evident in the patient's lifetime. From a histopathological point of view, these are real cancers but they are either progressing slowly or not at all, such that, if left, they would have never bothered the patient. They are commonly referred to as overdiagnosed cancers and their detection by tests for early diagnosis of cancer is referred to as over-diagnosis. False positive tests and over-diagnosis both cause some harm, which varies from minor discomfort occasioned by conduct of a biopsy to death in the rare case, for example, that a man with an overdiagnosed cancer dies as a result of complications of surgery aimed at curing it. In making decisions about PSA testing, the balance of the anticipated benefit – better health and extension of life due to early diagnosis – against the inevitable harm must always be taken into consideration. It is of paramount concern in this section of the guideline.

Strategies for PSA testing vary according to the age at which testing commences and ceases, the interval between tests, and the PSA threshold for further investigation (e.g. biopsy of the prostate). Protocols currently in use in Australia and elsewhere differ in all these variables.

Simple evaluative measures, such as a higher cancer detection rate, a shift in the stage distribution of cancer towards earlier stages or longer survival of people whose cancer was detected using the test, cannot be used to infer that testing achieves a better outcome from the cancer. Only demonstration of a reduction in mortality from cancer in people to whom the test is applied can provide certainty as to its efficacy. Randomised controlled trials are the only way in which such a reduction can be demonstrated confidently. In principle, they also provide the best evidence as to the extent of the associated harm. A systematic review of the available randomised controlled trials was the primary source of evidence used to answer PICO question 3.1.

Rigorous comparison of the performance of a range of different PSA testing strategies (e.g. with different age at testing, test interval, or biopsy criteria) to identify the optimal testing protocol would require many large randomised controlled trials with long follow-up periods. Since it is unlikely that such studies will be done, mathematical models have been developed that use information gained from the randomised controlled trials and other research to predict outcomes, both beneficial and harmful, of testing strategies that the randomised controlled trials have not evaluated specifically. We therefore also undertook a systematic review of relevant modelling studies to assist in answering PICO question 3.1.

If it is accepted, on the basis of evidence from randomised controlled trials, that a test such as the PSA test is able to deliver the desired outcomes, studies of comparative test performance (e.g. sensitivity, specificity, and positive predictive value) are useful in evaluating different approaches to achieving the desired outcomes. Such studies were used to provide evidence that might assist in answering PICO question 3.2, and have been used in a later section to assess the likely benefit or harm from adding DRE to PSA testing in deciding which men are at high risk of having a cancer that is not yet causing symptoms.

Once an efficacious test for early diagnosis of cancer is in widespread use in the community, observational epidemiological studies may be useful in evaluating its effectiveness in practice and in considering ways and means of improving its performance and achieving the best balance of benefits to harms. Such studies, however, are prone to a range of biases and should not be the primary basis for deciding whether or not to use such a test in the first place. Observational epidemiological studies were the main source of evidence reviewed for PICO question 3.3.

Evidence

Effect of testing strategies on rates of prostate cancer-specific death and metastases at diagnosis

Prostate cancer death reported in randomised controlled trials

Four randomised controlled trials[1][2][3][4][5][6][7][8] and one pseudo-randomised trial[9][10] were identified that investigated whether prostate cancer mortality is reduced by PSA testing in men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer. Three were judged to be at moderate risk of bias (the European Randomized Study of Screening for Prostate Cancer [ERSPC],[8] the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial [PLCO][3] and the Norrköping Randomised Controlled Trial of Prostate Cancer Screening[9]), and two were judged to be at high risk of bias (screening studies conducted in Stockholm [2] and Quebec[6]). The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

The largest of the trials was ERSPC,[8] a multicentre trial with seven centres. It found, in men aged 55–69 years, that PSA testing every 2–4 years (mostly without DRE and using a PSA level of > 3.0 ng/mL as an indication for biopsy), reduced prostate cancer-specific mortality compared with no testing (in reality background levels of testing): relative risk (RR) 0.79; 95% confidence interval (CI) 0.68–0.91 at a median of 11 years' follow-up. The other four trials[10][2][3][6] reported RRs of 1.01–1.16 at follow-up of 8–20 years. The most recent of these and by far the largest, the PLCO,[3] reported an RR of 1.09 (95% CI 0.87–1.36).

The five studies summarised above were also included in a contemporary meta-analysis of trials of PSA testing for prostate cancer.[11] The authors reported a summary relative risk of death from prostate cancer in men randomised to PSA testing of 1.00, 95% CI 0.86–1.17. They concluded that a pooled meta-analysis of the five included studies in this review identified that screening did not significantly decrease prostate cancer-specific mortality and is associated with a high degree of over-diagnosis, treatment and screening-related harms. They noted the overall heterogeneity in quality and study design of the five studies and gave greater weight to the four studies that did not find evidence of reduction in prostate cancer mortality than to the one study that did (ERSPC) in framing their conclusion.

Taken together, the results of the PLCO,[3] Norrköping,[10] Stockholm[2] and Quebec[6] trials are statistically incompatible with those of the ERSPC[8], either as used in the 2013 meta-analysis[11] (PLCO results from Andriole et al 2009[12] and ERSPC results from Schroder et al 2009[13]) or when updated with further experience of PLCO[3] and ERSPC[14]. A fixed effects meta-analysis of the PLCO, Norrköping, Stockholm and Quebec trial results from Figure 2 of Ilic et al (2013)[11], the four-studies' results to which Ilic et al gave greater weight in reaching their conclusion, gives an RR of 1.09, 95% CI 0.94–1.27 (p-value for heterogeneity among studies 0.91) for the risk of prostate cancer death in those offered testing relative to those not offered testing. This result compares with an RR of 0.84, 95% CI 0.73–0.95 from the ERSPC 2009 results as included in Ilic et al[11]. Note that the upper 95% confidence bound of the ERSPC estimate just overlaps the lower 95% confidence bound of the pooled four-studies results. Moreover, if the ratio of the four studies RR to the ERSPC RR is calculated, using the method of Altman et al[15], the value obtained is 1.30, 95% CI 1.06–1.58, which provides clear evidence that the results of the four studies are not statistically compatible with the ERSPC results. If we use the 2012 results of PLCO and ERSPC in these calculations instead of the 2009 results, the incompatibility is greater: the four studies RR of death from prostate cancer in those offered testing compared with those not offered testing becomes 1.08, 95% CI 0.94–1.24, the ERSPC 2012 result is 0.79, 95% CI 0.68–0.91. The lower 95% confidence bound of the former does not overlap the upper bound of the latter and the ratio of the two is 1.37, 95% CI 1.12–1.67, which provides strong evidence against the identicality of the two RR estimates.

Based on the above evidence that the results of the four studies and the results of the ERSPC are statistically incompatible, to proceed with formulation of a guideline for PSA testing the Expert Advisory Panel was constrained to assume that either the four studies were correct, or that the ERSPC was correct. The Panel preferred the ERSPC for the following reasons.

1. There are two aspects of study conduct that would cause PLCO to underestimate efficacy of PSA testing.[16] Of men randomised for PLCO, 44% had a PSA test in the 3 years before study entry, and an estimated 52% of men in the control arm had one in the period of the last intervention-group PSA test.[12] In comparison an estimated 30.7% of the ERSPC control group were tested once or more during the study (median of 9 years follow-up).[7] Further, 41% of PLCO intervention group men with a positive PSA test had a prostate biopsy within 1 year and 64% within 3 years of the test[17], while in the ERSPC biopsy compliance was approximately 86%[14].

2. The pattern of evolution of the difference in cumulative prostate cancer mortality between the ERSPC intervention group and control group is exactly that expected if PSA testing were efficacious in reducing prostate cancer mortality. There was little difference between the groups up to about 7 years from study entry; thereafter cumulative mortality diverged progressively, with the better outcome being in men offered PSA testing.[14]
3. There is a high degree of internal consistency in the ERSPC findings that adds to strength to the evidence it provides. While there was appreciable heterogeneity in the way the ERSPC was conducted in its seven component national centres, the relative risk (RR) of prostate cancer death in the intervention arm relative to the control arm in six of the seven centres was consistent with protection against prostate cancer death, ranging between 0.56 and 0.89.[14] The lowest RR (0.56) was in the Swedish (Gøteborg) centre, which offered testing every 2 years, not every 4 years as in the other centres; and the one outlier, an RR of 2.15, came from the small Spanish centre that, at the time of the analysis, had observed two deaths in the intervention arm and one in the control arm.[14] It is relevant to note, too, that the heterogeneity among the ERSPC centres was not statistically significant; the p-value for heterogeneity was 0.47. That is to say that the results from all seven centres are compatible statistically with the ERSPC RR for death from prostate cancer in men offered PSA testing of 0.79 (95% CI 0.68–0.91).

Should further research find that the ERSPC results are more unreliable than the Panel has judged them to be, it would have to reconsider its decision to prefer the evidence of the ERSPC and therefore this guideline.

In this context, it is relevant to note that the ERSPC published results up to 13 years of follow-up (previously 11 years) after the last date for the literature searches that contributed to the systematic reviews for this guideline.[18] Key features of the results summarised above, which are based on 11 years of follow-up, and those based on 13 years of follow-up are shown in Table 2.1.

Table 2.1. Summary of results of ERSPC study up to 11 years (as used for this guideline) and up to 13 years (published after last date of systematic review searches) in the core age group (55-69 years)

Results	Results up to 11 years of follow-up[8]	Results up to 13 years of follow-up[18]
Median follow-up (years)	11.0	13.0
Number of prostate cancer deaths in intervention group	299	355
Number of prostate cancer deaths in control group	462	545
Relative risk of death from prostate cancer – intervention group relative to control group	0.79 (95% CI 0.68-0.91)	0.79 (95% CI 0.69–0.91)
Absolute difference in risk of death from prostate cancer between intervention group and control group	-0.10 per 1,000 person years	-0.11 per 1,000 person years
Number needed to invite (NNI) to avert one prostate cancer death	1,055	781
Number needed to detect (NND) to avert one prostate cancer death	37	27

Sources: Schroder et al (2012)[8], Schroder et al (2014)[18]

There is little to no difference in the evidence for efficacy that these two analyses present, however there were material falls in the NNI and NND between analyses, which is explained by the accumulating difference in number of prostate cancer deaths between the intervention and control arms, which began at 6-7 years of follow-up and has grown from there.[8]

Metastases at diagnosis reported in randomised controlled trials

Three trials (ERSPC,[14] PLCO[3] and the Norrköping[9] trial) considered metastatic prostate cancer at diagnosis as a trial outcome. Two of these trials reported a lower risk of metastatic prostate cancer at diagnosis in the intervention arm than in the control arm:

- PLCO,[3] (RR 0.87; 95% CI 0.66–1.14) with a testing regimen consisting of annual PSA testing beginning at age 55 years and continued for 6 years (PSA > 4.0 ng/mL as the indication for biopsy) and with DRE for the first 4 years.
- ERSPC,[14] (RR 0.50; 95% CI 0.41–0.62) with testing regimens based on PSA testing every 2 or 4 years from age 50 or 55 years and continued for at least 12 years or until age 70 or 75 years, (PSA ≥ 3.0 ng/mL or ≥ 4.0 ng/mL as the indication for biopsy), with or without DRE. RRs for the four trial centres included in this analysis varied between 0.40 and 0.59.

Systematic PSA testing in men without prostate cancer or its symptoms was not associated with reduced risk of metastatic prostate cancer at diagnosis in the Norrköping trial[9] (RR 1.12; 95% CI 0.63–1.99). In this trial, testing began at age 50 years and continued every 3 years for 12 years. The first two tests consisted of DRE alone, and the third and fourth test included the combination of DRE and PSA testing (with PSA > 4.0 ng/mL as the indication for biopsy).

Overall, there is moderately consistent evidence that PSA testing, according to the range of strategies used in these trials, reduces the incidence of metastatic prostate cancer at diagnosis. The lower RR seen in the ERSPC trial,[14] compared with the PLCO[3] and Norrköping[9] trials, might indicate superiority of the PSA testing strategies used in the four ERSPC component studies analysed, which differed from the PLCO[3] and Norrköping [9] trials mainly in use of a PSA threshold for biopsy of > 3.0 ng/mL, not > 4.0 ng/mL.

Interpreting the randomised controlled trial findings

Given that greater reliance is being placed on the finding of the ERSPC[14], and that this trial showed a benefit for systematic PSA testing in men without prostate cancer or its symptoms, detailed consideration was given to the protocols followed to gain the observed effect. While the ERSPC centres varied in the detail of their testing protocols, they shared the following features:

- Each centre included men aged 55–69 years.
- The recommended screening interval was 4 years for all centres except Gøteborg, which used an interval of 2 years.

- A majority adopted PSA > 3.0 ng/mL without DRE as the criterion for referral for prostate biopsy, from the beginning or from the second round of testing.
- Each ceased testing at age 70–75 years.

Therefore, ERSPC results can be taken as indicative of the outcome of a policy of 2- to 4-yearly testing of men aged 55–69 years, referring men for biopsy when total PSA was > 3.0 ng/mL, and ceasing testing at age 70–75 years. While the published results of different ERSPC centres generally give little indication of consistent variation in effect due to variation in the testing protocol, the results from the Goteborg centre, which differed in offering testing at 2-year intervals from age 50 years, suggest that an earlier start and more frequent testing might be preferable to testing at 4-year intervals from age 55. In addition, in an all ages analysis of the ERSPC (Schroder et al 2012, Supplementary Appendix Table 5A), there was nothing to suggest efficacy of testing in men 70+ years of age (RR 1.18, 95% CI 0.81–1.72), although the confidence interval was wide.

Modelling studies

In addition to the evidence from randomised and pseudo-randomised controlled trials, three modelling studies [16][19][20][21] met the inclusion criteria for this review. They were studies in which participants had no history of prostate cancer or symptoms that might indicate prostate cancer at baseline (or that used state-transition models), and which compared two or more PSA testing strategies and reported benefits (e.g. prostate cancer-specific mortality, lives saved from prostate cancer or incidence of metastatic cancer at diagnosis) and harms (e.g. false positives or over-diagnoses of prostate cancer).

All three modelling studies were in English and published before 1 March 2014 (see Technical report). One study was based on the MISCAN model of cancer screening[20][21] and two were based on the Fred Hutchinson Cancer Research Center (FHCRC) microsimulation model of prostate cancer screening.[16][19] None of these studies was developed and calibrated for the Australian context, or validated in Australia. The MISCAN model was based on the Dutch population and calibrated mainly to Dutch and other European data, and levels of participation in testing were assumed to be 100%[19] and 80%.[20] The FHCRC studies were based primarily in the US population and were calibrated to US data, although one study[19] used initial treatment data for British Columbia, Canada. While not explicitly stated, it appears that both assumed 100% screening participation. Their simulated populations were, respectively, men with age distribution according to the European Standard Population,[21] men aged up to 100 years with age distribution according to the European Standard Population,[20] contemporary men in the USA aged 40 years,[16] and men in British Columbia aged 40 years.[19] Each model was expertly assessed as to its strengths and limitations across the domains of specifications, natural history, screening or triage recommendations and behaviours, diagnostic pathways, invasive cancer (survival, treatment) and costs (reference to rating scale). The strengths of both models, which included well-documented and relevant data sources and independent validations, were considered to outweigh their limitations, such as inadequate sensitivity analyses. As such, both models were found to adequately simulate prostate cancer incidence and mortality, with the caveats that neither model incorporated realistic screening behaviours (80% or 100% participation was assumed) and that the health outcomes presented for the MISCAN prostate cancer model were not adequately discounted in the assessment of quality-adjusted life years gained or lost.

Modelling to predict effect of testing protocols on outcome death from prostate cancer and balance of benefits and harms

Tables 2.2–2.4 describe the 47 different PSA testing protocols, with more than one protocol modelled in each of the three studies, and present the following outcomes:

- the probability that a man had one or more false positive PSA tests
- the probability that a man had an over-diagnosed prostate cancer (in this context a PSA-detected prostate cancer that would never have presented clinically in the man's lifetime had it not been detected by PSA testing)
- the probability that a man had death from prostate cancer prevented
- mean months of life gained per man tested
- number of prostate cancers needed to diagnose to prevent one death from prostate cancer (NND)
- mean months of life gained per man diagnosed as a result of testing, calculated as [*(mean months of life gained per man tested)* divided by *(probability that prostate cancer death is prevented, expressed as a percentage)* multiplied by 100 and divided by the NND].

These modelled outcome estimates provide a basis for selecting the protocol that, on present evidence, achieves the best balance between benefits and harms of PSA testing. Prevention of death from prostate cancer – the primary aim and main benefit of testing – is indicated by the probability that prostate cancer death is prevented. The harm to men who are tested is indicated by the probability of one or more false positive PSA tests and the probability of having an overdiagnosed cancer. 'Mean months of life gained per man diagnosed' measures the balance of benefit (life gained) to harm (over-diagnosis) as does, inversely, the ratio 'number of men overdiagnosed with prostate cancer per prostate cancer death prevented', which has been added in Table 2.4. Mean months of life gained per man diagnosed can also be interpreted as the expectation of life gained by each man diagnosed with and treated for prostate cancer as a result of PSA testing. It is strongly influenced by the probability of over-diagnosis; the more men there are over-diagnosed the more there are to 'share' the expectation of extension of life with men who actually experience the extension due to early diagnosis and treatment of a cancer that would otherwise have killed them. To assist in assessing the trade-offs between these outcomes, the testing protocols have been sorted in descending order by the probability that prostate cancer death is prevented. In addition, the testing protocol most like that of the ERSPC has been highlighted in each table to provide a directly evidence-based reference point with which to compare the possible alternative protocols.

Making protocol choices

Table 2.2 summarises the three alternative protocols based on the MISCAN model.[20] A change from 4-yearly to annual testing in this model predicts a 50% increase in probability of prevention of death from prostate cancer which is accompanied by a 22% increase in men with more than one false positive, a 55% increase in probability of over-diagnosis and a minimal fall in mean months of life gained per man diagnosed. Thus, the increase in benefit from the increase in testing frequency would appear to outweigh the additional harm.

Table 2.3 summarises protocols from the Pataky et al (2014)[19] model. Broadly it suggests that all protocols with higher probability of prevention of death from prostate cancer (up to 27% higher) achieve that at the cost of an increase in the percentage of men with more than one false positive, an increase in the probability of over-diagnosis and a reduction in means months of life gained per man diagnosed. Protocol 29 is an exception, however, where addition of testing in men 70–74 years, using a criterion for further investigation of 4.0 ng/mL instead of 3.0 ng/mL, is accompanied by a higher probability that death from prostate cancer is prevented, a fall in the percentage of men with more than one false positive, a fall in the probability of having an overdiagnosed prostate cancer and quite a small fall in mean months of life gained per man diagnosed.

Table 2.4 summarises the much larger number of protocols examined by Gulati et al (2013).[16] The most notable feature of these protocols is that use of > 95th percentile of PSA for age as the criterion for further investigation in place of a PSA > 4.0 ng/mL, with age range for testing and frequency of testing held constant, consistently results in a lower percentage of men with one or more false positive tests, a lower probability of having an overdiagnosed cancer and an appreciably higher mean months of life gained per man diagnosed, but with some reduction in the probability that death from prostate cancer is prevented. Therefore, there is a clear trade-off of reduction in benefit for reduction in harm with the use of > 95th percentile of PSA for age as the criterion for further investigation, but the generally high levels of mean months of life gained per man diagnosed when using these protocols suggest they may have a net beneficial effect. Thus, use of the > 95th percentile for age as the criterion for further investigation might be considered.

If we consider the ERSPC results as providing the best empirical evidence of which PSA testing protocol (if any) is efficacious in reducing mortality from prostate cancer, then we are left making choices between 55 and 50 years as the age at which to first offer a man PSA testing, offering testing at intervals of 4 or 2 years and ceasing to offer testing at 70 or 75 years of age. To aid in these choices we have extracted from Tables 2.2 to 2.4 comparisons of protocols that provide, most directly, the information we need to make those choices; these comparisons are in Table 2.5. In addition, to aid in the comparison, we have added to Table 2.5 comparative data for each pair of compared protocols, namely the difference in the percent of men having ≥ 1 false positive test and having an overdiagnosed cancer, difference in the percent of men having death from prostate cancer prevented, difference in the mean months of life gained per man diagnosed and the number of extra overdiagnosed cancers diagnosed per extra prostate cancer death prevented in going from the “less aggressive” (listed first in the pair) to the “more aggressive” protocol (listed second).

Beginning testing at 55 or 50 years of age

Only Pataky et al offer a comparison between a protocol beginning at 55 years of age and a protocol beginning at 50 years of age (Table 2.5), and in this comparison a change in testing frequency, from every 4 years to every 2 years, accompanies the change in age. Thus, while an unambiguous comparison between starting ages of 55 years and 50 years is not possible, the comparison made is advantageous because it compares the Goteborg protocol (starting at age 50 years and offering testing every 2 years) with the protocol followed by the other ERSPC centres (starting at age 55 and testing every 4 years). In summary, the Pataky et al model estimates that a change in starting age from 55 years to 50 years and an increase in testing frequency from every 4 years to every 2 years increases the probability of >1 false positive by 3.6%, increases the probability of over-diagnosis by 1% increases the number of prostate cancer deaths prevented by 18 per 10,000 (0.18%) and reduces the mean months of life gained per man diagnosed by 10.2 months. The number of extra overdiagnosed prostate cancers per extra prostate cancer death prevented is estimated at 5.6. It is not

possible, in this comparison, to say whether this higher cost in overdiagnosed cancers is mainly due to the change in age, the change in frequency of testing or largely shared between the two. Examination of the effects of change in frequency (4 years to 2 years) in Table 2.5, however, suggests that the change in age may be the dominant factor. Either way, this protocol change has, with the separately assessed change from testing every 4 years to testing every 2 years, the best balance of additional benefit to additional harm of the protocols compared in Table 2.5. While the reduction in mean months of life gained per man diagnosed, 10.2 months, is quite high, the mean months of life gained per man diagnosed for the protocol starting at 50 years of age, 34.1, remains reasonably high.

Extending testing from 69 to 75 years of age

The three relevant protocol pairs closest to the ERSPC protocol are summarised in Table 2.5. The pairs differ only in their PSA criteria for further investigation. Each protocol pair showed modest increases in the probabilities of ≥ 1 false positive test (3% to 6%), over-diagnosis (1.1% to 1.8%), and prostate cancer death prevented (13 to 20 per 10,000) when going from the cessation of testing at 70 to cessation at 75 years of age (the more aggressive option). The numbers of extra over-diagnosed cancers per prostate cancer death prevented, however, were high, 7 to 9, and are reflected in appreciable falls in the mean months of life gained per man diagnosed, -9.1 to -18.7, to comparatively low absolute levels, 22.1 to 29.1.

Testing every four years or every two years

The one model[19] that reported the impact of change in testing interval from 4 years to 2 years (in men aged 50–74 years, not 50–69 years) showed only small effects of the change. The proportion of men with ≥ 1 false positive test increased 0.7%, those with an over-diagnosed cancer also increased 0.7%, and there was a moderate increase in probability that prostate cancer death is prevented, 13 per 10,000 (Table 2.5). These results translate into in an estimated 5.4 extra over-diagnosed cancers per extra death from prostate cancer prevented by the change to the shorter interval. There was, however, little change, -0.5, in the mean months of life gained per man diagnosed. It appears, therefore, that the increase in prostate cancer deaths prevented by using a 2-year interval rather than a 4-year interval is well balanced against the increase in harm from false-positive PSA tests and over-diagnosis of prostate cancer.

Beginning testing at age 40 years

While not raised by variability in the ERSPC protocol, whether to offer testing first at 40 years of age (to obtain a PSA-based estimate of later risk of prostate cancer or to initiate regular testing) is a live issue. Gulati et al evaluated four protocols in which outcomes of testing from 50-69 and 40-69 years of age were compared at two different PSA criteria for further investigation, > 4 ng/mL and > 2.5 ng/mL (Table 2.5). For protocols testing men aged 40–69 years, the key outcomes (the probabilities of one or more false positive tests, over-diagnosed cancer, and prostate cancer death prevented, and the mean months of life gained per man diagnosed), were generally similar to those for protocols testing men aged 50–69 years. The increase in the probability that prostate cancer death is prevented by beginning testing at 40 years was small, at 2 to 3 in 10,000, and there were 5-7 extra overdiagnosed cancers per death prevented. In addition, because the increase in underlying prostate cancer mortality over 10 years from age 45–49 (7.98 per 100,000) is three times greater than that from age 40–44 (2.34 per 100,000), most of the small extra benefit would be gained by testing from age 45 (Table 2.7).

Modelling to predict effect of testing protocols on rates of metastatic prostate cancer at diagnosis

Heijnsdijk et al (2009)[21] modelled the effects of different test protocols on initial treatments, including palliative therapy, which can be taken as an indicator of metastatic disease present at the time of diagnosis. Relative to no testing, testing every 4 years from ages 55 to 70 years using a PSA threshold of 3.0 ng/mL resulted in a reduction of 2.1 men per 1,000 with metastatic disease at diagnosis at a cost of 150 unnecessary biopsies per 1000 men tested. With testing from 55 to 75 years every 4 years, the reduction in metastatic disease at diagnosis was 3.0 men per 1000 at a cost of 230 unnecessary biopsies per 1,000 men tested; and with testing at 55-70 years and a testing interval of 1 year, the reduction in metastatic disease at diagnosis was 2.6 men per 1,000 at a cost of 185 unnecessary biopsies per 1000 men tested.

Expressed in approximately equivalent terms to those of Table 2.3, increasing the frequency of testing from four-yearly to yearly increases the probability that diagnosis with metastatic prostate cancer is prevented by 0.06 percentage points (0.6 per 1,000) at a cost of increasing the probability of having an unnecessary biopsy by 3.6 percentage points, and extending the age range for testing to 75 years increases the probability that diagnosis with metastatic prostate cancer is prevented by 0.09 percentage points (0.9 per 1,000) at the cost of increasing the probability of having an unnecessary biopsy by 8.0 percentage points.

Table 2.2. Modelled outcomes of a range of PSA testing protocols sorted in decreasing order of probability of death from prostate cancer prevented for protocols reported by Heijnsdijk et al 2012

Protocol specifications				Outcomes*				
Ranking †	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥ 1 FP (%)	Probability of over-diagnosis (%)	Probability that prostate cancer death is prevented (%)	Mean months of life gained per man tested	NND
1	55–74	~3 ng /mL	1 year	57.3	7.2	1.10	0.98§	7
2	55–69	~3 ng /mL	1 year	44.8	4.5	0.90	0.88§	5
28 ERSPC ‡	55–69	~3 ng /mL	4 years	36.7	2.9	0.60	0.62§	5

Source: Heijnsdijk et al (2012)[20]

The protocol that most closely approximates the ERSPC testing strategy is shown highlighted. The protocols above it appear to perform relatively better in preventing death from prostate cancer.

~ Approximately

FP: false positive

*Outcomes were calculated as follows:

Probability of ≥ 1 FP % = percentage of men having one or more false positive tests over the age range of testing

Probability of over-diagnosis % = percentage of men having an over-diagnosed prostate cancer during the age range of testing

Probability that prostate cancer death is prevented % = percentage of men prevented from dying from prostate cancer from date of first testing to age 100 years[20]

Mean months of life gained per man tested = total months of life gained by men prevented from dying from prostate cancer averaged over all men tested

NND = Number of men needed to diagnose and treat for prostate cancer to prevent one death from prostate cancer (probability of over diagnosis % divided by the probability that death from prostate cancer is prevented %)

Mean months of life gained per man diagnosed = Mean months of life gained per man whose death from prostate cancer was prevented by testing divided by the NND (calculated as mean months of life gained per man tested divided by probability that prostate cancer death is prevented % multiplied by 100 and the result divided by the NND).

† Modelled protocols from all models were ranked in order of decreasing probability that prostate cancer death was prevented

§ Heijnsdijk et al (2012)35 did not provide an estimate of this value. It was estimated by using the following approach: life years gained (undiscounted) per 100 men tested multiplied by 12 and divided by 100.

‡ Protocol 28 approximates the testing strategy used in the intervention arm of ERSPC.[8]

Table 2.3. Modelled outcomes of a range of PSA testing protocols reported by Pataky et al 2014, sorted in decreasing order of probability of death from prostate cancer prevented

Protocol specifications				Outcomes*				
Ranking †	**PSA testing age range**	**Criteria for biopsy referral**	**Interval between PSA tests**	**Probability of ≥ 1 FP (%)**	**Probability of over-diagnosis (%)**	**Probability that prostate cancer death is prevented (%)**	**Mean months of life gained per man tested**	**NND**
10	40–74	PSA ≥ 3.0 ng /mL	2 years	22.8	3.4	0.70	0.81§	4.86
15	50–74	PSA ≥ 3.0 ng /mL	2 years	22.5	3.2	0.68	0.80§	4.71
16	50–74	PSA ≥ 3.0 ng /mL	2 years if PSA > median for age; 4 years if PSA < median for age	22.5	3.2	0.68	0.80§	4.73
		PSA ≥ 3.0 ng						

Protocol specifications				Outcomes*				
Ranking †	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥ 1 FP (%)	Probability of over-diagnosis (%)	Probability that prostate cancer death is prevented (%)	Mean months of life gained per man tested	NND
20	55–74	/mL	2 years	21.7	2.9	0.64	0.74§	4.57
23	60–74	PSA ≥ 3.0 ng /mL	2 years	22.1	3.2	0.63	0.69§	4.97
29	50–74	PSA ≥ 3.0 ng /mL up to age 69 years and PSA ≥ 4.0 ng /mL for men aged ≥ 70 years	2 years	17.4	2.3	0.60	0.74§	3.86
31	50–74	PSA ≥ 3.0 ng /mL	4 years	21.8	2.5	0.55	0.64§	4.57
32	50–69	PSA ≥ 3.0 ng /mL	2 years	19.1	2.1	0.55	0.71§	3.79
		PSA ≥ 3.0 ng /mL up to age 69 years and PSA						

Protocol specifications				Outcomes*				
Ranking †	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥ 1 FP (%)	Probability of over-diagnosis (%)	Probability that prostate cancer death is prevented (%)	Mean months of life gained per man tested	NND
43	50–74	≥ 4.0 ng /mL for men aged ≥ 70 years	4 years	15	1.4	0.44	0.57§	3.28
47 ERSPC ‡	55–69	PSA ≥ 3.0 ng /mL	4 years	15.5	1.1	0.37	0.49§	2.99

Source: Pataky et al (2014)[19]

The protocol that most closely approximates the testing strategy used by the ERSPC is shown highlighted. FP: false positive

*Outcomes were calculated as follows:

Probability of ≥ 1 FP % = percentage of men having one or more false positive tests over the age range of testing

Probability of over-diagnosis % = percentage of men having an over-diagnosed prostate cancer during the age range of testing

Probability that prostate cancer death is prevented % = percentage of men prevented from dying from prostate cancer from date of first testing to age 9034

Mean months of life gained per man tested = total months of life gained by men prevented from dying from prostate cancer averaged over all men tested NND = Number of men needed to diagnose and treat for prostate cancer to prevent one death from prostate cancer (probability of over diagnosis % divided by the probability that death from prostate cancer is prevented %)

Mean months of life gained per man diagnosed = Mean months of life gained per man whose death from prostate cancer was prevented by testing divided by the NND (calculated as mean months of life gained per man tested divided by probability that prostate cancer death is prevented % multiplied by 100 and the result divided by the NND).

‡ Protocol 32 approximates the testing strategy used in the Gøteborg centre of the ERSPC

§ Pataky et al (2014)[19] did not provide an estimate of this value. It was estimated by using the following approach: life years gained (undiscounted) per 100 men tested multiplied by 12 and divided by 100.

Table 2.4. Modelled outcomes of a range of PSA testing protocols reported by Gulati et al 2013, sorted in decreasing order of probability of death from prostate cancer prevented

Protocol specifications				Outcomes*				
Ranking †	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥ 1 FP %	Probability of over-diagnosis %	Probability that prostate cancer death is prevented %	Mean months of life gained per man tested	
3	40–74	PSA > 2.5 ng/mL or vPSA > 0.35 ng /mL per year	Annual (5 years if age < 50 years and PSA level < 1 ng/mL)	44	6	0.85	1.00	
4	40–74	PSA > 4.0 ng/mL or vPSA > 0.35 ng /mL per year	Annual	45	5.8	0.84	1.00	
5	50–74	PSA > 4.0 ng/mL or vPSA > 0.35 ng /mL per year	Annual	44	5.5	0.81	0.96	
6	40–74	PSA > 2.5 ng/mL	Annual	32	4.9	0.81	0.96	
7	50–74	PSA > 2.5 ng/mL	Annual	31	4.7	0.78	0.94	
8	40–74	PSA > 4.0 ng/mL	Annual	22	3.5	0.72	0.88	
9	40–74	PSA > 2.5 ng/mL	2 years	29	4	0.71	0.85	
11	50–74	PSA > 4.0 ng/mL	Annual	21	3.3	0.70	0.86	
12	50–74	PSA > 4.0 ng/mL	Annual (2 years if PSA level <2.5ng /mL)	21	3.3	0.70	0.86	

Protocol specifications				Outcomes*				
Ranking †	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥ 1 FP %	Probability of over-diagnosis %	Probability that prostate cancer death is prevented %	Mean months of life gained per man tested	
13	50–74	PSA > 2.5 ng/mL	2 years	29	3.8	0.69	0.84	5
14	40–74	PSA > 4.0 ng/mL or vPSA > 0.35 ng /mL per year	2 years	26	3.6	0.69	0.84	5
17	40–69	PSA > 4.0 ng/mL or vPSA > 0.35 ng /mL per year	Annual	41	3.9	0.67	0.89	5
18	50–74	PSA > 4.0 ng/mL or vPSA > 0.35 ng /mL per year	2 years	26	3.4	0.67	0.82	5
19	50–69	PSA > 4.0 ng/mL or vPSA > 0.35 ng /mL per year	Annual	40	3.7	0.65	0.85	5
21	40–74	PSA > 4.0 ng/mL	2 years	20	2.8	0.64	0.78	4
22	40–74	PSA > 95 th percentile for age§	Annual	16	2.4	0.64	0.83	1
24	40–69	PSA > 2.5 ng/mL	Annual	27	3.1	0.63	0.84	4

Protocol specifications				Outcomes*				
Ranking †	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥ 1 FP %	Probability of over-diagnosis %	Probability that prostate cancer death is prevented %	Mean months of life gained per man tested	
25	50–69	PSA > 2.5 ng/mL	Annual	27	2.9	0.61	0.82	
26	50–74	PSA > 4.0 ng/mL	2 years	20	2.7	0.61	0.77	
27	50–74	PSA >95th percentile for age§	Annual	15	2.3	0.61	0.81	
30	45–74	PSA > 4.0 ng/mL	2 years (5 years if PSA level < median for age)	19	2.4	0.58	0.75	
33	40–69	PSA > 4.0 ng/mL	Annual	17	2	0.54	0.75	
34	40–74	PSA > 95th percentile for age§	2 years	14	1.8	0.54	0.73	
35	40–69	PSA > 2.5 ng/mL	2 years	24	2.2	0.52	0.72	
36	50–69	PSA > 4.0 ng/mL	Annual	17	1.8	0.51	0.73	
37	40–69	PSA > 95th percentile for age§	Annual	15	1.7	0.51	0.73	
38	50–74	PSA > 95th percentile for age§	2 years	14	1.7	0.51	0.70	
		PSA > 4.0 ng/mL or						

Protocol specifications				Outcomes*				
Ranking †	PSA testing age range	Criteria for biopsy referral	Interval between PSA tests	Probability of ≥ 1 FP %	Probability of over-diagnosis %	Probability that prostate cancer death is prevented %	Mean months of life gained per man tested	
39	40–69	vPSA > 0.35 ng /mL per year	2 years	21	1.9	0.50	0.71	
40 ERSPC (Gøteborg) ‡	50–69	PSA > 2.5 ng/mL	2 years	23	2	0.49	0.70	
41	50–69	PSA >95th percentile for age§	Annual	14	1.5	0.48	0.71	
42	50–69	PSA >4.0 ng/mL or vPSA > 0.35 ng /mL per year	2 years	20	1.8	0.47	0.67	
44	40–69	PSA > 4.0 ng/mL	2 years	15	1.4	0.43	0.64	
45	40–69	PSA > 95th percentile for age§	2 years	13	1.3	0.42	0.63	
46	50–69	PSA > 4.0 ng/mL	2 years	14	1.3	0.41	0.61	

Source: Gulati et al (2013)[16]

The protocol that most closely approximates the protocol used by the ERSPC is shown highlighted.

FP: false positive vPSA: PSA velocity *Outcomes were calculated as follows:
Probability of ≥ 1 FP % = percentage of men having one or more false positive tests over the age range of testing
Probability of over-diagnosis % = percentage of men having an over-diagnosed prostate cancer during the age range of testing
Probability that prostate cancer death is prevented % = percentage of men prevented from dying from prostate cancer from date of

first testing to the end of life31

Mean months of life gained per man tested = total months of life gained by men prevented from dying from prostate cancer averaged over all men tested

NND = Number of men needed to diagnose and treat for prostate cancer to prevent one death from prostate cancer (probability of over diagnosis % divided by the probability that death from prostate cancer is prevented %)

Mean months of life gained per man diagnosed = Mean months of life gained per man whose death from prostate cancer was prevented by testing divided by the

NND (calculated as mean months of life gained per man tested divided by probability that prostate cancer death is prevented % multiplied by 100 and the result divided by the NND).

† Modelled protocols from all models were ranked in order of decreasing probability that prostate cancer death was prevented

§95th percentiles were 2.5, 3.5, 4.5 and 6.5 ng/mL for ages 40–49, 50–59, 60–69 and 70–74 years, respectively.

‡ Protocol 28 approximates the testing strategy used in the Gøteborg centre of the ERSPC[8]

Table 2.5. Comparisons of outcomes of testing using different ages at testing (55–69 years or 50–69 years; 50–69 years or 50–74 years; 50–69 or 40–69 years) and different intervals between tests (4 years or 2 years) with the PSA criterion for investigation and the other PSA testing protocol components (interval between tests or age at testing) held constant

Comparison	Protocol specifications			Modelled protocol outcomes*				
PSA testing age (years)	Criteria for biopsy referral	PSA testing interval	≥ 1 false positive (%)	Over-diagnosis (%)	Probability that prostate cancer death is prevented (%)	Mean months of life gained per man diagnosed	Over-diagnosed cancers per prostate cancer death prevented	≥ 1 false positive (%)
Outcomes of testing in med aged 55-69 and 50-69 years†	55-69	≥ 3.0 ng/mL	4 years	15.5	1.1	0.37	44.3	3.0
	50-69	≥ 3.0 ng/mL	2 years †	19.1	2.1	0.55	34.1	3.8
Outcomes of testing in men aged 50-	50-69	> 2.5 ng/mL	2 years	23	2	0.49	34.7	4.1
	50-74	> 2.5 ng/mL	2 years	29	3.8	0.69	22.1	5.5
	50-69	≥ 3.0 ng/mL	2 years	19.1	2.1	0.55	34.1	3.8
	50-74	≥ 3.0 ng/mL	2 years	22.5	3.2	0.68	25.0	4.7

Comparison	Protocol specifications			Modelled protocol outcomes*				
69 and 50-74 years††	50-69	> 4.0 ng/mL	2 years	14	1.3	0.41	47.8	3.2
	50-74	> 4.0 ng/mL	2 years	20	2.7	0.61	29.1	4.4
Outcomes of testing men every 4 years and every 2 years ‡	*50-74	≥ 3 ng /mL	4 years	21.8	2.5	0.55	25.5	4.5
	*50-74	≥ 3 ng /mL	2 years	22.5	3.2	0.68	25.0	4.7
Outcomes of testing in aged 50-69 and 40-69 years‡‡	50-69	> 4.0 ng/mL	2 years	14	1.3	0.41	47.8	3.2
	40-69	> 4 ng /mL	2 years	15	1.4	0.43	46.8	3.3
	50-69	> 2.5 ng/mL	2 years	23	2	0.49	34.7	4.1
	40-69	> 2.5 ng/mL	2 years	24	2.2	0.52	33.0	4.2

†Criterion for biopsy but not interval between tests held constant. Data source: Pataky et al (2014)34.

††Interval between tests and criterion for further investigation held constant. Data sources: Gulati et al (2013)31 and Pataky et al (2014) 34.

‡Age and criterion for further investigation held constant. Data source: Pataky et al (2014)34.

‡‡Interval between tests and criterion for further investigation held constant. Data source: Gulati et al 201331.

*Model results for ages 50–74 years are presented because results for 50–69 years have not been reported.

†No additional protocols that would permit PSA testing interval to be held constant.

Sources: Gulati et al (2013)[16], Pataky et al (2014)[19] (Data extracted from Tables 2.3 and 2.4 to facilitate the comparisons.)

Effect of different testing strategies on rates of biopsy-diagnosed prostate cancer

To examine and quantify the effect of different testing strategies on rates of biopsy-diagnosed prostate cancer, a systematic review was done that encompassed studies of men with no history of prostate cancer who had undergone a prostate biopsy less than 1 year after a PSA test and were participants in a prostate cancer screening RCT or in an NHMRC level of evidence III-2 or higher fully paired diagnostic performance study that permitted comparison of the diagnostic performance of two or more different PSA thresholds ≤4.1ng/mL or two different prostate cancer screening protocols, and achieved specified minimum levels of diagnostic confirmation and results reporting.

Seven level III-2 diagnostic performance studies met the inclusion criteria.[22][23][24][25][26][27][28] All were at moderate risk of bias. In addition results from an analysis of relevant ERSPC data[29] have been included for comparative purposes only; it did not meet all inclusion criterion as only men with an elevated PSA were biopsied and the biopsy was a sextant biopsy.

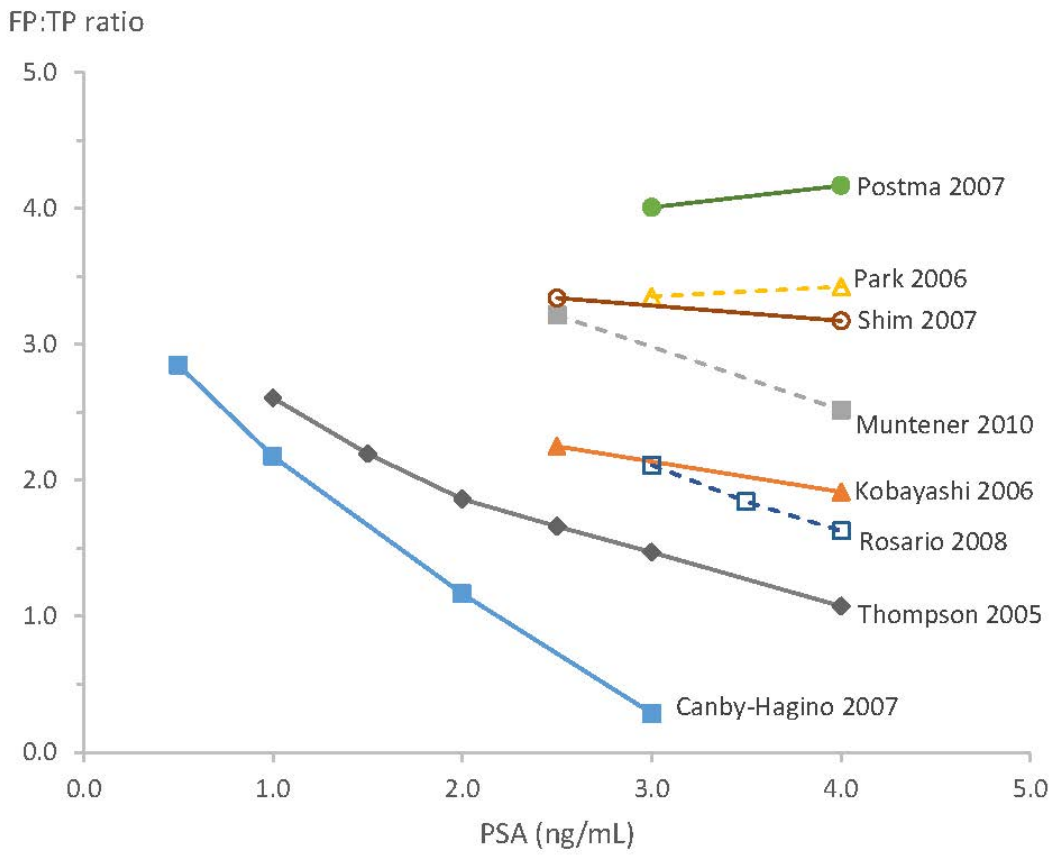
In one study, the placebo arm of the Prostate Cancer Prevention Trial,[26] men were biopsied regardless of PSA level or DRE, enabling comparisons of sensitivity and specificity at different PSA thresholds. In this study, men with a normal DRE and PSA levels at baseline were tested annually for 7 years and offered a sextant biopsy at the end of the trial.[26] Potential verification bias was considered and shown not to be an issue.[26]

The remaining studies were able to provide estimates only of increases in numbers of cancers detected and numbers of unnecessary biopsies with decreasing PSA thresholds.[22][23][24][25][27][28][29] In six of these studies all men underwent prostate biopsy if their PSA levels exceeded specified thresholds. Participants were diverse, ranging from men with lower urinary tract symptoms to asymptomatic participants in population-based screening programs.[22][23][25][27][28][29] In the remaining study, all men with a family history of prostate cancer and a PSA below a specified PSA threshold underwent prostate biopsy.[24]

The published studies did not describe how the PSA assays used were calibrated. For two studies, World Health Organization (WHO) calibration could be inferred from information available on the assay (Izotope) manufacturer's website.[23][27] Two studies did not report the PSA assay used.[22][28] Only one study compared yields stratified by Gleason score at different PSA thresholds.[26]

Comparisons between studies in terms of absolute numbers were limited due to differing biopsy protocols, populations and PSA assays and their calibration. Therefore, this review focuses on the effects of varying thresholds within studies. In all studies, lowering the PSA threshold increased cancer detection at a cost of increased unnecessary biopsies[22][23][24][25][26][27][28][29] In six of the eight studies, the ratio of false positives to true positives increased as the PSA threshold changed from 4.0 ng/mL to 3.0 or 2.5 ng/mL (Figure 2.1). In two studies in which lower PSA levels were assessed, the ratio of false positives to true positives increased more rapidly as the threshold was reduced from 3.0 ng/mL to 2.0 ng/ml, and even more rapidly again as it was reduced from 2.0 ng/mL to 1.0 ng/mL. The ratio of false positives to true positives varied across the studies from 1.1 to 4.2 at a PSA threshold of 4 ng/mL (Figure 2.1). Lowering the PSA threshold from 4.0 ng/mL to 3.0 ng/mL resulted in estimates of 2.17–3.77 additional unnecessary biopsies for every additional cancer detected.[23][26][28][29]

Figure 2.1. Plots of false positive to true positive ratios at each PSA threshold in the eight studies reviewed



Sources: Data from Postma et al (2007),[29] Park et al (2006),[23] Shim et al (2007),[27] Muntener et al (2010),[22] Kobayashi et al (2006),[25] Rosario et al (2008),[28] Thompson et al (2005),[26] Canby-Hagino et al (2007).[24]

The Prostate Cancer Prevention Trial[26] provided the most comprehensive data. In its placebo arm sample of repeatedly tested men aged over 54 years, lowering the PSA threshold from 4.0 to 3.0 ng/mL resulted in an 11.7 percentage-point increase in sensitivity and a 7.1 percentage-point decrease in specificity, 26 additional cancers detected and 56 additional unnecessary biopsies per 1000 men tested, giving 2.17 additional unnecessary biopsies per additional cancer detected.[26] When the threshold was lowered from 3.0 ng/mL to 2.0 ng/mL41, there was a further 20.4 percentage-point increase in sensitivity and a 14.2 percentage-point decrease in specificity, with 2.48 additional unnecessary biopsies for every additional cancer detected.[26] Similar effects were seen in a cohort of men with PSA less than 4.0 ng/mL and a family history of prostate cancer.39 Further lowering of the threshold from 4.0 to 2.5 ng/mL or from 3.0 to 2.5 ng/mL in the Prostate Cancer Prevention Trial [26] resulted in 2.26 and 2.39 additional unnecessary biopsies for every additional cancer detected, respectively. [26]

The sensitivity for detecting higher-grade cancers increased when the PSA threshold was lowered from 4.0 ng /mL, and these increases were greater than those for the detection of any cancer:[26] lowering the PSA threshold to 3.0 ng/mL increased the sensitivity for identifying any cancer by 11.7 percentage points, whereas the sensitivity for identifying cancers with Gleason score > 6 increased by 17.2 percentage points, and for identifying cancers with Gleason score > 7 increased by 17.5 percentage points. Similarly, lowering the PSA threshold to 2.5 ng/mL increased sensitivity for identifying any cancer by 20.0 percentage points, whereas the sensitivity for identifying cancers with a Gleason score > 6 increased by 26.8 percentage points, and for identifying cancers with a Gleason score > 7 increased by 28.0 percentage points. Further reduction to 2.0 ng /mL did not result in greater increases in sensitivity for detecting higher grade disease.[26]

Considerable weight has been given to the Prostate Cancer Prevention Trial study.[26] However, there are two caveats to the application of these results to population-based prostate cancer testing in Australia. First, participants had PSA levels of 3.0 ng/mL or less, a normal DRE and an American Urological Association symptom score less than 20 prior to the start of annual testing and, thus, may not represent a general population of men in the relevant age group. Secondly, Hybritech PSA assays were used and, while it was not reported how these assays were calibrated, Hybritech calibration was probably used. As PSA measurements vary with assay type and calibration, the absolute values for PSA measurements reported in the Prostate Cancer Prevention Trial study[26] may not be directly applicable to the Australian context, in which over 95% of laboratories use the WHO calibration and the most commonly used assays are the Roche and Abbott assays.

Using a PSA test result at a particular age to inform subsequent PSA testing

Two level III-2 studies[30][31] reported the risk of prostate cancer mortality according to PSA levels in men younger than 56 years. One was a retrospective cohort study of participants in the Copenhagen City Heart Study.[30] This study was at moderate risk of bias for PSA levels at ages 45–49 and 50–54 years and at high risk of bias for PSA levels at ages less than 45 years. The second study was the larger Malmö Preventive Project,[31] which was at high risk of bias. It used a retrospective cohort design to assess the risk associated with PSA levels at age 51–55 years, and a nested case-control design to assess the risk associated with PSA levels at 37.5–42.5 years and 45–49 years. For the latter design, absolute risk was imputed and the imputation was validated in the cohort group.

This review focused on men from approximately age 40–55 years at testing and a maximum of 20 years follow-up, since its primary purpose was to obtain data relevant to PSA testing over a period of approximately 20 years from first testing. In the Copenhagen City Heart Study,[30] blood was sampled in 1981–1983 and PSA testing introduced into clinical practice in Denmark in 1995. Thus, informal PSA screening was unlikely to have affected 10-year risks of prostate cancer mortality. In the Malmö Preventive Project[31] blood was sampled from 1974–1984 for the case-control study and 1980–1990 for the cohort study. On the basis of Swedish PSA testing data,[31] the authors assumed that testing rates remained low (up to 5%) up until 1998 (8 years prior to end of study) and therefore that it was unlikely that any informal or opportunistic screening could have substantively affected prostate cancer mortality 15 and 20 years after PSA measurement. Given their retrospective designs, baseline PSA levels could not have affected prostate cancer diagnosis in either of these studies.[30][31]

The studies[30][31] took place in Danish and Swedish populations (not primarily high-risk populations) that were followed up primarily in the pre-PSA era, when more effective definitive treatments may have been less readily available or offered than in Australia today. However, given that these are populations of European origin, as are a majority of Australians, and that the studies relate primarily to the natural history of a disease in relation to a risk indicator, they may reasonably be taken to represent the evolution of prostate cancer risk in Australia in relation to PSA levels measured on blood taken prior to the beginning PSA testing for the early detection of prostate cancer.

Table 2.6 summarises estimates of increments in absolute percentage cumulative risk of prostate cancer death above the risk at a baseline PSA of < 1 ng/mL[30] or the lowest quarter of the PSA distribution[31] by age, length of follow-up and baseline PSA level. While the Copenhagen City Heart Study[30] reported on cumulative risk for three additional PSA levels (from > 3.0 to 4.0 ng/mL, from > 4.0 to 10.0 ng/mL, and > 10.0 ng/mL), increments in risk at these levels are not shown because the lower bound of the top 10% of the PSA distribution in the Malmö Preventive Project[31] lay consistently in the range 1.0–3.0 ng/mL. The results in the table show the following:

- Risk increments for comparable baseline PSA levels in the Copenhagen City Heart Study[30] at 10 years and the Malmö Preventive Project 46 at 15 years are similar but tend to be higher in the Malmö Preventive Project,[31] as would be expected from the longer follow-up. Thus, within the limits of this comparison, the findings of these two studies appear similar.
- Risk increments for PSA levels in the top quarter and top 10% of the distribution in men aged 37.5–42.5 years in the Malmö Preventive Project[31] are small (0.1% to 0.8%) for both 15 and 20 years of follow-up and only a little more at 25 years (0.60% and 1.13%).
- These increments are 1–2 times greater at 15 years of follow up and 3–4 times greater at 20 years of follow up in men aged 45–49 years, and 6–12 times greater at both 15 and 20 years of follow up in men aged 51–55 years.
- RRs of death from prostate cancer over 20 years of follow-up in the Malmö Preventive Project[31] were similar whether the blood in which PSA was tested was collected at age 37.5 to 42.5 years (RR 3.4 for the highest quarter and 9.0 for the highest tenth of PSA with reference to the lowest quarter of PSA), 45–49 years (RR 4.9 and 10.1), or 51–55 years (RR 5.2 and 10.0). While there is a little more variation between age groups in these figures after 25 years of follow-up, this is probably due to chance, given the small number of deaths studied (162) and the wide confidence intervals for the cumulative risk estimates (e.g. the reference cumulative risk level was 0.1; 95% CI 0.01–0.69, for men aged 37.5 to 42.5 years). The RRs over 10 years of follow-up reported from the Copenhagen City Heart Study[30] were also similar in the three age groups.

Table 2.6 Estimates of increments in absolute percentage cumulative risk of prostate cancer death above the risk at a baseline PSA of < 1 ng/mL (Orsted et al, 2012) or the lowest quarter of the PSA distribution (Vickers et al 2013) by age, length of follow-up and baseline PSA level

			Reference PSA level	Compared PSA level

Study	Age (years)	Length of follow-up (years)	PSA level	Cumulative risk % of prostate cancer death to the end of follow-up	PSA level	Increment in cumulative risk % of prostate cancer death to the end of follow-up (cumulative risk at compared PSA level minus cumulative risk at reference level)	Relative risk of prostate cancer death to the end of follow-up
Orsted et al, 2012	< 45	10	≤ 1.0 ng/mL	0.3	> 1.0-2.0 ng /mL	0.3	2.0
					> 2.0-3.0 ng /mL	1.2	5.0
Vickers et al, 2013	37.5-42.5	15	Lowest quarter, ≤ 0.42 ng/mL	0.1	Highest quarter, ≥0.90 ng/mL	0.12	2.2
					Highest tenth, ≥1.30 ng/mL	0.5	6.0
		20		0.1	Highest quarter, ≥0.90 ng/mL	0.24	3.4
					Highest tenth, ≥1.30 ng/mL	0.8	9.0
		25		0.1	Highest quarter, ≥0.90 ng/mL	0.6	7.0
					Highest tenth, ≥1.30 ng/mL	1.13	12.3
Orsted et al, 2012	45-49	10	≤ 1.0 ng/mL	0.4	> 1.0-2.0 ng /mL	0.6	2.5
					> 2.0-3.0 ng /mL	2.0	6.0
					Highest quarter, ≥ 1.1 ng/mL	0.23	3.9

					Highest tenth, ≥ 1.6 ng/mL	0.66	9.2
Vickers et al, 2013	45-49	15	Lowest quarter, ≤ 0.44 ng/mL	0.08			
		20		0.24	Highest quarter, ≥ 1.1 ng/mL	0.94	4.9
					Highest tenth, ≥1.6 ng/mL	2.18	10.1
		25		0.52	Highest quarter, ≥ 1.1 ng mL	2.15	5.1
					Highest tenth, ≥ 1.6 ng/mL	4.62	9.9
Orsted et al, 2012	50-54	10	≤ 1.0 ng/mL	0.5	> 1.0-2.0 ng /mL	0.8	2.6
					> 2.0-3.0 ng /mL	2.7	6.4
Vickers et al, 2013	51-55	15	Lowest quarter, ≤ 0.53 ng/mL	0.33	Highest quarter, ≥ 1.4 ng/mL	1.47	5.4
					Highest tenth, ≥ 2.4 ng/mL	3.05	10.2
		20		0.57	Highest quarter, ≥ 1.4 ng/mL	2.41	5.2
					Highest tenth, ≥ 2.4 ng/mL	5.11	10.0
		25		0.94	Highest quarter, ≥ 1.4 ng/mL	4.13	5.4
					Highest tenth, ≥ 2.4 ng/mL	8.09	9.6

Sources: Orsted et al (2012)[30], Vickers et al (2013)[31]

PSA testing strategies in high-risk groups

There is little or no empirical evidence to support any particular modification of a PSA testing protocol to apply to men at high risk of prostate cancer. The approach taken in most guidelines for PSA testing is to recommend that men at high risk for prostate cancer begin testing at an earlier age than men at average risk (typically at age 45 years), whereas men at average risk are advised to begin testing at age 50 years. This is a rational approach because men at high risk have, depending on their risk factors, an increased risk at each age that is likely to be a constant multiple (RR for the risk factor in question[ii]) of the risk in men at average risk. Therefore,

it should be possible to identify an age earlier than 50 years at which risk in men with a particular risk factor would be the same as the average risk at age 50 years, and from which risk would be expected to evolve with age in the same way as it would evolve from age 50 years in men at average risk. In principle, by beginning PSA testing at this age, high-risk men could expect the same benefit, and probably the same harm, from testing as average-risk men starting testing at age 50 years.

Using present incidence or mortality rates for prostate cancer, it is arguably not possible to identify accurately the age at which men at, for instance, twice the average risk of prostate cancer would have the same underlying risk of prostate cancer occurrence or death as average-risk men at age 50. This is for two reasons:

- Present incidence rates are strongly influenced by testing lead time and over-diagnosis, which depend on the intensity of PSA testing in the population.
- Mortality rates have fallen, at least partly because of PSA testing.

Each of these factors will have an effect on the relationship of age with prostate cancer incidence and mortality because of the strongly age-determined frequency of PSA testing. Therefore, in seeking to determine an age at which high-risk men might be advised to begin PSA testing that is equivalent to a recommended age of 50 years for average-risk men, we chose to focus on the annual average prostate cancer mortality rates for Australia in 1991 to 1995, the 5-year period of peak prostate cancer mortality. This peak occurred shortly after PSA testing began in Australia and, thus, rates for 1991–1995 are unlikely to have been influenced by PSA testing. Mortality is considered to be more relevant than incidence in this context, because it is the hazard that PSA testing aims to prevent.

Table 2.7 provides estimates of the increase in prostate cancer mortality in average risk men over the succeeding 10 years of their lives from ages 40, 45 and 50 years (based on 1991–1995 Australian mortality rates, which are approximately those that obtained before PSA testing in Australia could have had an effect on mortality).[32] For ages 40 and 45 only, Table 2.7 also includes estimates for men with varying levels of higher than average risk of prostate cancer (RR 2.0–5.0). A period of 10 years of life was chosen because most recent included results of the ERSPC indicate that most of the mortality reduction achieved through PSA testing is evident at 10–11 years after start of testing.[8]

Table 2.7 indicates that a 45-year-old man at three times the average risk of prostate cancer would have an increase in his annual risk of prostate cancer death of 23.9 per 100,000 over the next 10 years of his life from the very low rate at age 45 years. This increase is a little higher than the corresponding increase for an average-risk man starting PSA testing at age 50 years (22.7 per 100,000), and would therefore provide as much justification, in terms of risk of death from prostate cancer, for offering PSA testing to a 45-year-old man at three-times the average risk of prostate cancer as there is for offering it to a 50-year-old man at average risk of prostate cancer. For a man at 2.5 times average risk, the increase in annual risk of prostate cancer death over the next 10 years is 20.0 per 100,000, which is somewhat less than that for the 50-year-old at average risk, but probably sufficient to justify offering PSA testing to a 45-year-old at 2.5 times the average risk of prostate cancer. Following the same logic, in 40-year-old men, a case can be made for offering testing to those whose risk is 9–10 times average risk (corresponding to increases in annual risk of prostate cancer death over the next 10 years of life of 21.1 and 23.4 per 100,000 respectively) or more.

Table 2.7. Estimated increase in prostate cancer-specific mortality rate (annual number of deaths per 100,000 men) over the next 10 years for Australian men aged 40, 45 and 50 years who are at average risk of prostate cancer, and those who are at two- to ten-fold increased risk of prostate cancer

Relative risk of prostate cancer	Mortality rate		
Age 40 (mortality at age 50 minus mortality at age 40)	**Age 45 (mortality at age 55 minus mortality at age 45)**	**Age 50 (mortality at age 60 minus mortality at age 50)**	
1.0 (average risk)	2.3	8.0	**22.7***
2.0	4.7	16.0	
2.5	5.8	20.0	
3.0	7.01	23.9	
3.5	8.2	27.0	
4.0	9.3	31.9	
5.0	11.7	40.9	
6.0	14.0		
7.0	16.4		
8.0	18.7		
9.0	21.1		
10.0	23.4		

*This value is provided as a point of reference with which to compare the increases in prostate cancer mortality over the next 10 years in men aged 40 and 45 years at various degrees of increased risk of prostate cancer.

Source: Data from Australian Institute of Health and Welfare (2014) [32]

Evidence reviewed in Chapter 1 and summarised in Table 1.1 addresses the increase in RR of prostate cancer conferred by different degrees of family history of prostate cancer. In brief, men with a brother or multiple first-degree relatives diagnosed with prostate cancer have a more than 2.5- to 3-fold increased risk of death due to prostate cancer. Men with three affected first-degree relatives have an 8- to 10-fold increased risk of prostate cancer death. It is important to note, however, that the confidence intervals about these estimated higher levels of RR are wide and are compatible with relative risks as low as 4 and as high as 19 (based on RRs for men with a family history of three first-degree relatives with a diagnosis of prostate cancer). This evidence, together with the information in Table 2.7, has been used in formulating the recommendation relating to men at high risk of prostate cancer.

Evidence summary and recommendations

Evidence summary	Level	References
For men aged 55–69 years without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, prostate cancer-specific mortality was reduced by PSA testing every 2–4 years using total PSA > 3.0 ng/mL as the threshold for biopsy. The reduction in mortality may be greater in men aged 50-69 years offered testing every 2 years.	II, III-2	[1], [2], [9], [10], [8], [33], [7], [6], [5], [4], [12], [3]
While the modelling studies were not considered to provide evidence independent of the empirical data on which they were based, they offer a guide to how changes in specific parameters (age, testing interval and threshold for biopsy) affect the balance of benefits to harms. Modelled comparisons suggested that change in starting age from 55 to 50 years and a reduction in testing interval from 4 years to 2 years increases the number of prostate cancer deaths prevented by 18 per 10,000 men at an additional cost in overdiagnosed cancers of 1%; that is, an extra 5.6 overdiagnosed cancers per extra prostate cancer death prevented. There is also a reduction in mean months of life gained per man diagnosed of 10.2 months, but the mean months of life gained per man diagnosed for the protocol starting at 50 years of age and testing every 2 years remains reasonably high at 34.1 months. Modelled comparisons also suggested that the number of over-diagnosed cancers per prostate cancer death prevented in men tested at ages 70–74 (7.0 to 9.0 in three relevant protocols) when testing ended at age 74 years instead of 69 years was substantially more than the average number of over-diagnosed cancers per prostate cancer death prevented when testing only from 50 to 69 years (3.2 to 4.1 for the same protocols). The mean months of life gained per man diagnosed with testing at ages 70–74 was also about one-third less than when testing only to 69 years. A modelled comparison of testing 2-yearly with testing 4-yearly (with age held constant at 50–74 years and threshold constant at ≥ 3.0 ng/mL) estimated a 0.13 percentage-point gain in the probability of prostate cancer death prevented, at the expense of a 0.7 percentage-point increase in the probability of ≥ 1 false positive test, a 0.7 percentage-point increase in the probability of over-diagnosis of prostate cancer, and a 0.5 month reduction in the mean months of life gained per man diagnosed with prostate cancer. Modelled comparisons suggested there was little benefit gained from starting regular testing at age 40 rather than at age 50 (an increase of 0.02 to 0.04 percentage points in the probability that prostate cancer death is prevented).	N/A	[16], [19], [20], [21]

Evidence summary	Level	References
Note: NHMRC classification of levels of evidence does not currently encompass modelling studies.		
As the PSA threshold for referral to biopsy was reduced from 4.0 ng/mL, the ratio of false positive to true positive tests increased. The rate of increase in this ratio appeared to become greater as the threshold PSA level was progressively reduced. Thus, any reduction made in PSA threshold from 4.0 ng/mL was accompanied by an increasingly adverse trade-off of more true positive tests (greater sensitivity) for more false positive tests (lower specificity).	III-2	[22], [23], [24], [25], [26], [27], [28], [29]
In men aged 37.5–42.5 years, absolute differences in cumulative risk for prostate cancer between men with PSA levels in the top quarter and the top 10% of the PSA distribution and men with PSA levels in the bottom quarter of the distribution were small at 15 years of follow-up (+0.1% and +0.5%) and a little more at 20 years of follow-up (+0.2% and +0.8%). In men aged 45–49 years, these differences were greater (+0.2% and +0.7%) at 15 years of follow-up and more so at 20 years of follow-up (+0.9% and +2.2%). They were greater again in men aged 51–55 years: 1.5% and 3.1% at 15 years and 2.4% and 5.1% at 20 years. RRs for prostate cancer death in men in the highest quarter and highest tenth of PSA, relative to men in the lowest quarter, out to 20 and 25 years of follow-up after an index PSA test, varied little by age when the blood for PSA testing was taken.	III-2	[30], [31]

Evidence-based recommendation[?]	Grade
For men at average 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.	**C**

Consensus-based recommendation[?]

If the necessary data become available and the required processes put in place to ensure effective implementation, consider replacing > 3.0 ng/mL with > 95th percentile for age as the criterion for further investigation.

Consensus-based recommendation[?]

Do not offer PSA testing at age 40 years to predict risk of prostate cancer death.

Consensus-based recommendation[?]

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 at average risk of prostate cancer.

Consensus-based recommendation[?]

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.[iii]

[iii] This Consensus-based recommendation assumes testing with the criterion for further investigation a PSA of ≥ 3 ng/mL. This recommendation will be a high priority for reconsideration when the Australian model of PSA testing has been completed. For example, use of the 95th percentile for age in place of ≥ 3 ng/mL might improve appreciably the balance of harms to benefits of testing in men 70–74 years of age.

Consensus-based recommendation[?]

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.

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.

Offer testing from age 50 years according to the protocol for men who are at average risk of prostate cancer.

For recommendations on further investigations, see 2.5 Testing with variants of PSA to improve sensitivity after an initial total PSA ≤ 3.0 ng/mL and 2.6 Testing with variants of PSA or repeat PSA testing to improve specificity after an initial total PSA > 3.0 ng/mL.

Expected benefits and harms from recommended PSA testing

Informing men of the benefits and harms of testing is a key component of the recommendations regarding PSA testing. To aid their use in practice, therefore, we have compiled Table 2.8, a quantitative table of estimated harms, benefits and measures of the balance and harms and benefits associated with two of the testing protocols, testing from age 50 or age 45 in average risk men. This table can be used when informing men of the benefits and harms of testing and the trade-offs that a decision in favour of testing would entail. It is based on results of the best available mathematical modelling studies, which we have used elsewhere in this guideline. Ideally, the results would have been produced especially for this guideline and based on an Australian model. This is not yet possible but will be soon.

It was not considered to be possible to add the protocol for testing men at higher than average risk to Table 2.8 since this issue has not yet been dealt with in published reports of the adequate quality models.

Table 2.8. Modelled estimates of harms, benefits and balance of harms to benefits of recommended PSA testing protocols

Recommendation	Protocol specifications			Modelled protocol outcomes			
Harms of testing		Benefits of testing		Balance of harms to benefits			
PSA testing age (years)	Criterion for further investigation	PSA testing interval	Probability of ≥ 1 false positive PSA test (%)	Probability of over diagnosis of prostate cancer (%)	Probability that prostate cancer death is prevented (%)	Mean months of life gained per man tested	Mean months of life gained per man diagnosed with prostate cancer
Testing from 50 years of age in men at average risk of prostate cancer†	50-69	PSA ≥ 3 ng /mL	2 years	19	2.1	0.55	0.71
Testing from 45 years of age in men at average risk of cancer‡	45-69	PSA ≥ 3 ng /mL	2 years	23	2.1	0.50	0.72

*Probability of harms is estimated over the duration of the testing protocol; benefits are estimated over the lifetime from the age testing started.

†Estimates of harms, benefits and balance based on modelling results for this protocol were from Pataky et al (2014)[19]

‡Estimates of harms, benefits and balance based on averages of the above results for 50-69 years obtained by Pataky et al (2014)[19] and results for a protocol for testing men 40-69 years of age every 2 years with a criterion for further investigation of > 2.5 ng/mL obtained by Gulati et al (2013)[16]. Most likely effect of the lower criterion PSA value is to over-estimate the probability of > 1 false positive PSA test.

Health system implications of these recommendations

Clinical practice

Despite a recommendation by the Royal College of Pathologists of Australasia to repeat PSA testing at intervals of 2 years or 4 years, depending on the result,[34] it is probable that many men currently having PSA testing are tested annually. Therefore, the recommendation to offer PSA testing every 2 years in men aged 50–69 years who wish to undergo testing after being informed of the benefits and harms of testing could lead to less frequent testing and fewer false positive tests. Misuse or new safety concerns from these recommendations are

not envisaged. An increase in litigation alleging malpractice is possible given the benchmark these recommendations provide and the known frequency of practice that does not align with them, particularly with respect to assurance that men tested have been informed of the benefits and harms of testing. This potential legal risk will be mitigated by robust efforts to ensure that knowledge of the guideline is disseminated to all relevant health practitioners and the development of aids that will assist them in practising according to the guideline.

Resourcing

Implementation of the recommendation for a 2-year interval between PSA tests for men aged 50–69 years who wish to undergo testing could reduce the costs of testing, reduce the frequency of false positive tests and reduce consequent investigation and its cost.

Barriers to implementation

No barriers to implementation of these recommendations are foreseen.

Footnotes

[i] Clinical questions were translated into the PICO framework: population, intervention (or exposure), comparator and outcome (see Appendix 3).

[ii] In this section, RR refers to a presumed unbiased estimate of the RR for prostate cancer. As noted in **Chapter 1**, studies of risk factors that are strongly believed or well known to put men at high risk for prostate cancer, such as a family history of prostate cancer, are likely to produce positively biased estimates of RR of prostate cancer incidence because of a higher likelihood that men thought to be at high risk will request or be offered PSA tests, often starting at a younger age, and have a risk of incident prostate cancer that is boosted by over-diagnosis. Correspondingly, estimates of RR of prostate cancer mortality are likely to be negatively biased due to earlier diagnosis of otherwise potentially fatal prostate cancer, although probably less so. While these matters do not influence the logic of this section, they need to be taken into consideration when deciding whether or not a particular risk factor should lead to a change in the PSA testing protocol, as proposed in the recommendations arising from this chapter. The recommendation for PSA testing strategies in men at higher-than-average risk of prostate cancer (below) is based on evidence on the RR of prostate cancer mortality associated with family history of prostate cancer, not the RR of prostate cancer incidence associated with it (**Chapter 1 Risk**), given that the former is likely to be the less biased estimate of relative risk.

[iii] This Consensus-based recommendation assumes testing with the criterion for further investigation a PSA of ≥ 3 ng/mL. This recommendation will be a high priority for reconsideration when the Australian model of PSA testing has been completed. For example, use of the 95th percentile for age in place of ≥ 3 ng/mL might improve appreciably the balance of harms to benefits of testing in men 70–74 years of age.

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Discussion

Supporting attachments

Preface

Prostate cancer has emerged as the second-most important cause of cancer death in Australian men. This has encouraged increasing efforts to diagnose potentially fatal prostate cancer while still confined to the prostate, as this offers the best opportunity for treatment to eradicate it.

Measurement of prostate-specific antigen (PSA) in serum has largely replaced the traditional method of detecting prostate cancer early, the digital rectal examination. However, while PSA testing is widely used, there is still debate over whether it offers men net benefit. PSA is specific to the prostate but not for cancer. Consequently, establishing PSA levels that will detect most cancers without prompting too many unnecessary biopsies is challenging. A marker that is specific for cancer would be ideal, but none has yet been found. Moreover, if a specific marker is identified, the problem remains that indolent cancers would be better not found. Gleason grade can predict cancer behaviour, but it is not perfect either and its assessment requires a prostate biopsy.

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Yet it remains that prostate cancer kills men. Notwithstanding the problems of PSA testing, men still seek testing in the hope of avoiding death from prostate cancer.

In developing these guidelines, we have used systematic methods to determine from extensive, relevant scientific literature how PSA can be best used to find prostate cancer early, and how the next steps in decision-making about care can maximise the potential benefits and minimise the potential harms from PSA testing. These guidelines have been purpose-developed for Australia, occasionally drawing on existing evidence-based guidelines such as those developed by the UK National Collaborating Centre for Cancer. Consensus and clarity have emerged in most areas; in others, promising approaches to management have been identified that need further study before they can be accepted as the standard of care.

We are indebted to Prostate Cancer Foundation of Australia, Cancer Council Australia, members of the Expert Advisory Panel, subcommittee, systematic reviewers and all other contributors. All made vital contributions to developing these guidelines.

Professor Villis Marshall AC
Chair, Expert Advisory Panel
Clinical practice guidelines for PSA testing and early management of test-detected prostate cancer

Prostate biopsy and multiparametric MRI

When prostate biopsy is indicated for men with suspected prostate cancer, the optimal protocol for investigation involves determining:

- criteria for an adequate prostate biopsy
- which further investigations, if any, are indicated if prostate cancer is not found in an adequate initial biopsy.

The use of multiparametric magnetic resonance imaging (MRI) in men with elevated prostate-specific antigen (PSA) levels who have not yet undergone an initial biopsy is beyond the scope of this guideline.[i]

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Footnote

[i] This chapter focuses on the use of multiparametric MRI after a negative prostate biopsy, not on its use for the primary investigation of a positive PSA test, because this is not routine clinical practice.

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Contents

Chapter 3 Prostate biopsy and multiparametric MRI

Discussion

Unresolved issues

The following issues remain unresolved:

- the predictive value of histopathological features reported by the pathologist reviewing the initial biopsy
- whether the transrectal and transperineal biopsy approaches differ according to effectiveness in cancer detection, comparability of biopsy findings with subsequent prostatectomy findings, or rates of adverse outcomes
- comparative complication rates for various biopsy schemes. Few studies reported complication rates for various biopsy schemes and these were mainly immediate outcomes. Data for long-term follow-up findings were difficult to match to biopsy pattern.
- the role of multiparametric MRI, given that it cannot identify all prostate tumours, including all clinically significant tumours.

Studies currently underway

There is a large volume of studies assessing the role of multiparametric MRI in biopsy of the prostate and reporting on the use of new or existing biomarkers.

Future research priorities

Molecular signatures of cancer, including those for prostate cancer, are increasingly recognised. Further research is needed to establish the place of multiparametric MRI in the context of both evolving imaging technologies and the increasing understanding of molecular oncology – in particular, the use of multimodal MRI in combination with other imaging modalities like ultrasound and functional imaging (positron emission tomography). Such research will allow more precise image-guided targeted biopsies of the prostate in the determination of significant prostate cancers.

Risk

For Australian men, has a family history of prostate cancer been shown to be reliably associated with a 2.0-fold or greater increase in risk of occurrence of or death from prostate cancer when compared to men who do not have a family history of prostate cancer? **(PICO[i] question 1)[ii]**

In order to help men who are considering prostate-specific antigen (PSA) testing to make an informed decision and tailor their choices based on individual risk, it is necessary to assess factors associated with an increased risk of diagnosis of, or death from, prostate cancer. While many modifiable and non-modifiable risk factors for prostate cancer have been investigated, few have been clearly shown to be strongly associated with increased risk.[1] Fewer studies still have specifically assessed the risks for Australian men.

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This chapter only considers family history as a risk factor for prostate cancer. Family history was considered because it is common for PSA testing guidance to recommend that men who have a family history of prostate cancer, and who decide to be tested, should commence testing at a younger age (usually 40 or 45) than men without a family history. Other risk factors, such as ethnicity, will be considered in future editions of this guideline.

PSA testing strategies in high-risk groups outlines an approach that can be applied to any risk factor.

Contents

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.[2] 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.[3] A number of international guidelines on prostate cancer screening recommend that men with a family history of prostate cancer commence the informed decision making process [4] or testing[5] at an earlier age than men at average risk of prostate cancer (i.e. men without a family history).

The PSA level of a man's first PSA test is also associated with subsequent risk of prostate cancer. It has been suggested that baseline PSA testing for men in their forties is a useful way of identifying men who are at high risk of prostate cancer.[6] The evidence for PSA level as a risk factor is reviewed in Chapter 2 (see Using a PSA test result at a particular age to inform subsequent PSA testing).

Chapter 2 includes PSA testing recommendations relating to family history of prostate cancer and to PSA as a risk factor for prostate cancer.

Evidence

Eleven retrospective cohort studies [7][8][9][10][11][12][13][14][15][16][17] and one nested case-control study[18] addressing the question and meeting the inclusion criteria were included in the systematic review: three used linked population-wide data from Sweden,[13][14][10] five used the Swedish Family-Cancer Database,[7][8][12][15][16] and one each used linked data from Utah in the USA,[18] Southern Sweden,[9] Iceland,[11] and Finland[17]. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

All 11 retrospective cohort studies [7][8][9][10][11][12][13][14][15][16][17] (level III-2 evidence) that reported the risk of incident prostate cancer were of low quality, with a high risk of bias due to inadequate length of follow-up for the diagnosis of prostate cancer and inadequate control for potential confounding factors. Notably, none controlled for potential PSA testing bias resulting from the fact that men who have a close relative diagnosed with prostate cancer may be more likely to request a PSA test and then be diagnosed with prostate cancer. Similarly, the nested case-control study[18] (level II evidence) was also low quality with a high risk of bias.

Three of the retrospective cohort studies[15][7][8] also reported the risk of death from prostate cancer. These studies were assessed to be low quality with a high risk of bias, due to an inadequate length of follow-up.

Prostate cancer diagnosis

The results were very consistent across studies that assessed risk of a prostate cancer diagnosis for men with a particular level of family history. Two studies [11][18] that assessed family history in third-degree relatives[iii] each reported a relative risk (RR) of approximately 1.2, with 95% confidence intervals that included 1 or had a lower limit close to 1. For family history in second-degree relatives, the same two studies[11][18] reported RRs of 1.3–1.4 and 1.7 (with a lower 95% confidence limit below 1) when the affected relative was diagnosed before age 55–60 years.

For men with affected first-degree relatives, the RRs were generally greater than 2.0 (which is considered clinically important) and statistically significant. Men with a first-degree relative (father or brother) diagnosed with prostate cancer had approximately double the risk of being diagnosed with prostate cancer, compared with men without this family history or the general male population. The RR was higher for men aged less than 50–55 years, those whose first-degree relative was diagnosed before age 68 years and those with multiple affected first-degree relatives. While there was some inconsistency across studies, the increased risk was less than 2.0-fold for those aged approximately 75–80 years or over.

The observed association between family history and the probability of being diagnosed with prostate cancer may be affected by increased PSA testing in the exposed group. None of the studies directly addressed the potential impact of increased PSA testing of asymptomatic men with a positive family history. Data from the population-based Prostate Cancer Database Sweden[10] reported stronger associations between family history and diagnosis of Stage 1c prostate cancer (which is detected after a PSA test) and diagnosis closer to the time of that of the family member (within 1 year). In all but one of the studies reviewed,[13] the period of observation for the diagnosis of prostate cancer fell within the PSA testing era (after 1990).

Because of this potential confounding by PSA testing of the association between family history and diagnosis of prostate cancer, it may be misleading to use the RRs of prostate cancer *incidence* in men with a family history to determine whether a change in the testing protocol is warranted (see Chapter 2 Testing). Studies that report RRs based on prostate cancer-specific *mortality* rates are probably more reliable, although a small negative bias might be expected from the likely protective effect of PSA testing against prostate cancer death. Therefore in this review, we have focused on the estimates of the RR for death from prostate cancer for men with a family history.

Prostate cancer-specific mortality

Three studies[7][8][15] reported the association between risk of death from prostate cancer and levels of family history (Table 1.1). Men whose fathers had been diagnosed with prostate cancer were approximately twice as likely to die from prostate cancer, compared with men without a first-degree relative diagnosed with prostate cancer. Men with a brother diagnosed with prostate cancer were at 2.8-fold increased risk of dying from prostate cancer, and this increased to 3.3-fold when the brother was diagnosed before age 60 years.

The risk of dying from prostate cancer was higher when two first-degree relatives were diagnosed: the risk was 3 times higher for men with a father and a brother diagnosed with prostate cancer, 6 times higher if two brothers were diagnosed with prostate cancer, and 7 times higher for men whose father and a brother had died from prostate cancer. The risk of dying from prostate cancer was 8–10 times higher for men with three first-degree relatives diagnosed with prostate cancer.

In summary, men with first-degree relatives (father and/or brother/s) diagnosed with prostate cancer had at least double the risk of dying from prostate cancer than men without this family history. The relative increase in risk was greater when multiple first-degree relatives were affected, especially multiple brothers, when a brother was diagnosed before age 60 years, or when both the father and a brother had died from prostate cancer.

Table 1.1. Relative risk of dying from prostate cancer for men with a first-degree relative diagnosed with prostate cancer, compared with those without a first-degree relative diagnosed with prostate cancer or the general male population

Level of family history of prostate cancer	Relative risk for prostate cancer death*	95% confidence interval	p-value
1 first-degree relative			
Father diagnosed	1.8	1.6–2.0	< 0.0001
Father diagnosed age < 60 years	2.1	1.0–4.3	0.06
Father died	2.0	1.8–2.4	< 0.05
Brother diagnosed	2.8	2.3–3.3	< 0.0001
Brother diagnosed age < 60 years	3.3	2.3–4.6	< 0.0001
Brother died	2.8†	1.9–3.8	< 0.05
2 first-degree relatives			
Father and brother diagnosed	3.0	2.0–4.4	< 0.0001
2 brothers diagnosed	6.3	3.8–10.5	< 0.0001
Father and brother both died	6.9	2.6–18.3	< 0.0001
3 first-degree relatives			
Father and 2 brothers diagnosed	9.7	4.1–23.4	< 0.0001
3 brothers diagnosed	8.1	2.0–32.5	0.003

**compared with men with no father or brother diagnosed with prostate cancer for all rows except where specified*

†compared with the general population

Sources: Brandt et al (2010),[7] Brandt et al (2012)[8]

Interpreting the findings

None of the studies were conducted in Australia. The generalisability and applicability of their findings to the Australian setting may be affected by a number of factors, including the degree to which PSA testing is used for screening asymptomatic men, and genetic factors (the majority of studies were conducted in Sweden). In addition, differences in the patterns of prostate cancer treatment may affect prostate cancer-specific mortality rates.

The effect of family history on the risk of prostate cancer-specific mortality is considered in Chapter 2.

Evidence summary and recommendations

Evidence summary	Level	References
Risk of prostate cancer diagnosis Men with a first-degree relative (father or brother) diagnosed with prostate cancer had approximately double the risk of being diagnosed with prostate cancer than men without this family history. This RR was higher for younger men, those whose first-degree relative was diagnosed at a younger age, and those with multiple first-degree relatives diagnosed with prostate cancer. While there was some inconsistency across studies, the RR was less than 2 for those aged approximately 75–80 years or over. The RR was 1.3–1.4 for men with only second- or third-degree relatives diagnosed with prostate cancer. Uncontrolled confounding by PSA testing is likely to bias estimates of RR of prostate cancer incidence upwards.	II, III-2	[7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18]
Risk of death from prostate cancer Men with a first-degree relative (father or brother) who was diagnosed with prostate cancer had a 2- to 3-fold increased risk of dying from prostate cancer compared with men without this family history. Compared with no family history, the RR of death from prostate cancer was 6- to 10-fold greater if multiple first-degree relatives were diagnosed with prostate cancer (two or three brothers, or two brothers and father), or if the brother and father had died from prostate cancer.	III-2	[7], [8], [15]

Note on the recommendations based on this evidence

No direct recommendations were formulated based on this evidence because it serves to identify risk, not to evaluate the effects of interventions to manage this risk. This evidence on risk informed the recommendations in Chapter 2.

PSA testing strategies in high-risk groups includes a consensus-based recommendation for PSA testing of men whose risk of prostate cancer is estimated to be at least 2.5–3 times higher than average and for men whose risk is estimated to be at least 9–10 times higher than average due to any risk factors, including family history. No separate recommendation was made about PSA testing in men with risk factors that increase risk by a factor of less than 2.5–3 times average risk. The Expert Advisory Panel considered that this lesser degree of risk may not be sufficient to justify a change in the evidence-based PSA testing strategy recommendation for men at average risk, after taking into consideration the need to balance the potential benefits and harms of PSA testing.

Discussion

Footnotes

[i] Clinical questions were translated into the PICO framework: population, intervention (or exposure), comparator and outcome (see Appendix 3).

[ii] For the current edition of this guideline, the scope of this clinical question was limited to family history. At the next edition, this systematic review will be updated and expanded to include other risk factors such as genetic factors (e.g. *BCRA1, BCRA2, HOXB13 G84E*, Lynch syndrome genes).

[iii] First-degree relatives comprise fathers, brothers and sons. Second-degree relatives include grandfathers, uncles, nephews and grandsons. Third-degree relatives include cousins and great-grandfathers.

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Supporting attachments

Discussion

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Chapter 1 Risk

Discussion

Unresolved issues

The degree to which increased PSA testing of asymptomatic men with a family history of prostate cancer contributes to, or explains, their observed increased probability of being diagnosed with prostate cancer is unknown.

Future research priorities

The contribution of increased PSA testing of asymptomatic men with a family history to the observed increased probability of being diagnosed with prostate cancer needs to be quantified. This could be achieved through long-term prospective cohort studies of Australian men.

Role of digital rectal examination

For men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer what is the incremental value of performing a digital rectal examination (DRE) in addition to PSA testing in detecting any prostate cancer? **(PICO[i] question 4)**

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Background

DRE, in combination with measurement of serum prostatic acid phosphatase, was the standard method for establishing the clinical suspicion of prostate cancer prior to the introduction of PSA testing and systematic biopsy of the prostate. However, men were often reluctant to have a DRE and remain so today. Other problems were that a significant volume of cancer needed to be present before a DRE abnormality could be identified, and that there was significant observer variation. Therefore, in an era when PSA testing is 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.

Evidence

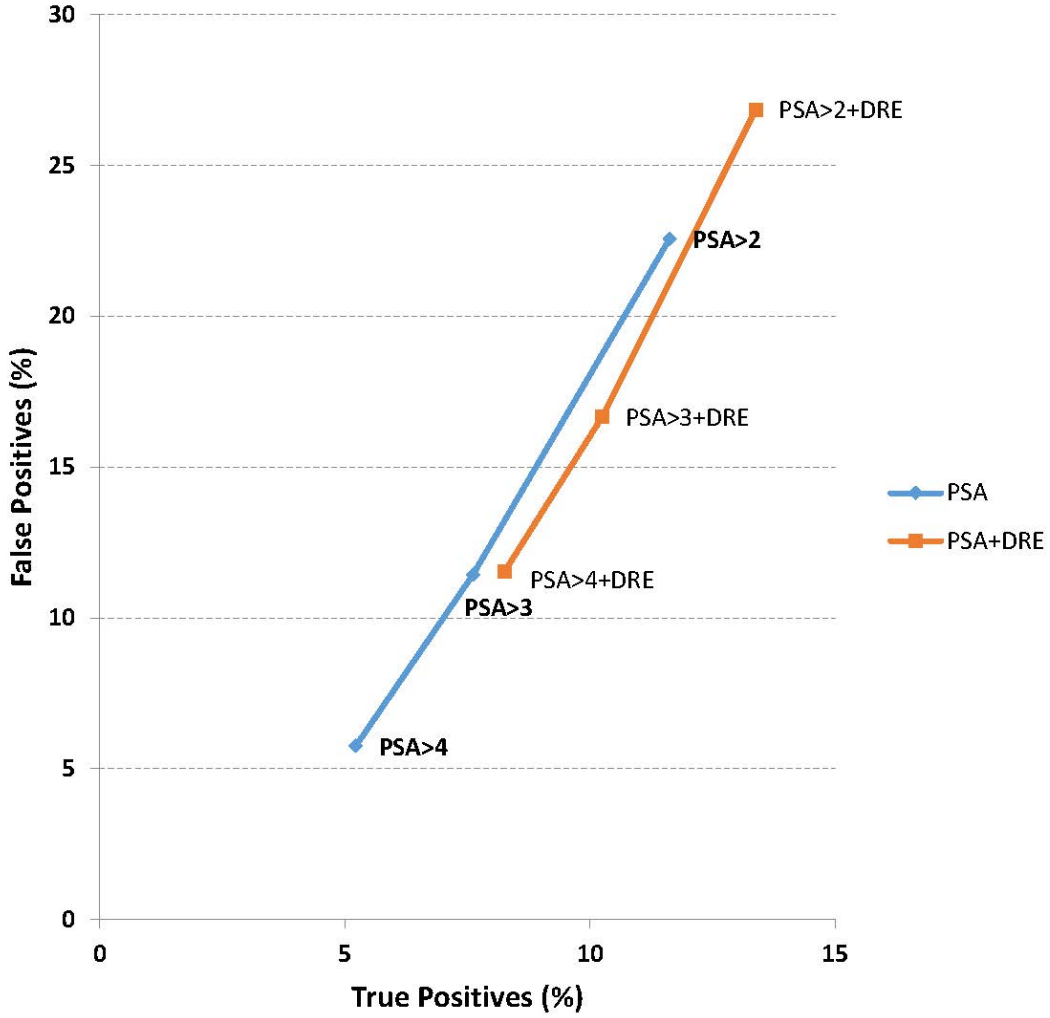
Five studies[1][2][3][4][5] were identified that examined the benefits and harms of using DRE in addition to total PSA levels as initial tests to identify men likely to have prostate cancer. All the studies were assessed to have a moderate risk of bias. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

The most important data were provided by the Prostate Cancer Prevention Trial,[5] a randomised controlled trial comparing finasteride with placebo, in which men underwent testing for 7 years. This was the largest relevant screening study identified, and the only one in which men were biopsied regardless of DRE result or PSA level (i.e. screen-negatives as well as screen-positives were biopsied). Therefore, this study was able to provide reliable

estimates of differences in sensitivity and specificity, as well as estimates of increases in cancers detected and unnecessary biopsies. The study was generally well conducted, with potential verification bias investigated and shown not to be an issue.[6] However, the risk of bias was considered to be moderate because the authors did not state whether DRE, PSA tests and pathologist review of biopsy specimens were performed blind. To avoid potential bias due to any possible effects of finasteride, only data from the placebo arm were examined in this review.

The use of DRE in addition to PSA thresholds resulted in a moderate increase in the detection of prostate cancer.[5] However, the incremental gain in cancer detection was at the cost of biopsy referrals for men without prostate cancer (false positives); the rate of false positives increased with decreasing PSA threshold. The rate of false positives was 1.91 for every additional cancer using a PSA threshold of 4.0 ng/mL, 1.99 for every additional cancer using a threshold of 3.0 ng/mL, and 2.44 for every additional cancer using a threshold of 2.0 ng/mL. At a threshold of 3.0 ng/mL, adding DRE resulted in a relative increase in sensitivity of 12 percentage points, accompanied by a specificity decline of 7 percentage points. In absolute terms, this would mean that for every 1000 men repeatedly tested, 26 more cancers would be found, but 52 more false positives would be referred for biopsy. At a PSA threshold of 4.0 ng/mL, there was a 14 percentage-point increase in sensitivity and a 7 percentage-point decline in specificity. In absolute terms, 30 more cancers would be detected but 58 men would undergo unnecessary biopsies per 1000 men tested. Importantly, the same increase in cancer detection rate could have been achieved without DRE by simply using a lower PSA threshold (Figure 2.2).

Figure 2.2. Trade-off between detecting true positives and adding false positives for PSA alone and in combination with DRE



Source: data derived from Thompson et al (2007)[5]

The other four studies[1][3][4][2] examined the addition of DRE to a PSA threshold of 4.0 ng/mL. The results of these studies were roughly in agreement as to the direction and magnitude of accuracy of the incremental gain. The number of false positives for every additional cancer detected was even higher in these studies, despite the use of more extensive biopsies in one study,[3] and the fact that DRE was performed by urologists or urologic residents in three of these studies.[1][3][4] However, differences in populations, the frequency of testing, and verification prevent pooling of the data and limit direct comparison.

Four studies[1][2][4][5] reported the effects of adding DRE to a testing protocol with PSA threshold of 4.0 ng/mL on cancer yield stratified by Gleason score:

- Data from the placebo arm of the Prostate Cancer Prevention Trial[5] show that, for every 1000 men tested, adding DRE to a testing protocol with PSA threshold of 4.0 ng/mL would detect three additional cancers with Gleason score > 7 and seven additional cancers with Gleason score > 6. The proportion of higher-grade cancers amongst the additional cancers detected with DRE (23.2% cancers with Gleason score > 6 and 9.0% cancers with Gleason score > 7) was lower than, or similar to, that detected using PSA alone (35.2% cancers with Gleason score > 6 and 10.1% cancers with Gleason score > 7).
- A study conducted among US veterans[2] reported that 34.0% of the additional cancers detected by DRE were Gleason score > 6 and 13.6% were Gleason score > 7.
- In a large US community screening study,[1] 3.3% of additional cancers detected by DRE were Gleason score > 7.
- In a small Mexican screening study[4] the single additional cancer detected by DRE had a Gleason score of 7.

However, based on the data from the Prostate Cancer Prevention Trial,[5] the addition of DRE to PSA increased sensitivity for cancers with Gleason score > 7 by 25.4 percentage points, while specificity was reduced by 8.6 percentage points. For cancers with Gleason score > 6, the addition of DRE to PSA gained a 15.0 percentage-point increase in sensitivity at the cost of a 8.5 percentage-point reduction in specificity.

The findings of the Prostate Cancer Prevention Trial[5] may not be generalisable to the Australian primary care setting because the trial cohort was comprised of men over 55 years old who had undergone previous screening (initial normal DRE and PSA < 3 ng/mL on entry to the study). In comparison, PSA testing in Australia covers a broader range of men. In addition, the trial investigators may have benefited from specific training and have had greater experience in performing DRE, compared with clinicians who perform DRE in Australian primary care. Therefore, the benefits of adding DRE to PSA testing in Australia may be fewer than those reported.

Evidence summary and recommendations

Evidence summary	Level	References
There is evidence from one large moderate-quality study that the addition of DRE to PSA testing provided an incremental gain in prostate cancers detected, but at a cost of two or more extra false positives per cancer detected. The study also showed that similar gains could be made by lowering the PSA threshold. DRE accuracy is likely to be lower outside the trial setting of this study.	III-2	[1], [3], [4], [2], [5]
The sensitivity for detecting high-grade cancers was increased when DRE was added to PSA testing. However, the gain in detecting higher-grade cancers by adding DRE was generally not greater than that for lower-grade cancers.	III-2	[1], [4], [2], [5]

Evidence-based recommendation[?]	Grade
In asymptomatic men interested in undergoing testing for early diagnosis of prostate cancer, digital rectal examination is not recommended as a routine addition to PSA testing in the primary care setting.	**C**

Practice point[?]
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.

Health system implications of these recommendations

Clinical practice

Current guidelines for preventive care in general practice[7] recommend both DRE and PSA for men who choose to undergo prostate cancer testing after being fully informed of the benefits, harms and uncertainties of testing. Therefore, implementation of this recommendation would alter current practice.

Misuse or new safety concerns from these recommendations are not envisaged. The Evidence-based guideline may reduce litigation alleging malpractice when a diagnosis of prostate cancer is perceived to have been delayed as a consequence of a primary-care practitioner’s non-performance of a DRE.

Resourcing

Implementation of this recommendation would have no significant resource implications. It may slightly reduce the consultation time for men attending primary care.

Barriers to implementation

No barriers to the implementation of this recommendation are foreseen.

Footnote

[i] Clinical questions were translated into the PICO framework: population, intervention (or exposure), comparator and outcome (see Appendix 3).

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Discussion

Sociocultural apects of PSA testing in Australia

Guidelines developed in partnership with

This chapter provides general information on sociocultural factors relevant to prostate-specific antigen (PSA) testing and the management of early prostate cancer. These include socioeconomic status, geographical factors, and ethnocultural factors including those relevant to Aboriginal and Torres Strait Islander men.

Search terms to identify evidence relevant to Aboriginal and Torres Strait Islander peoples were included in the systematic reviews for each clinical question, but no relevant evidence was identified for any question (see Technical report). Hence, there was insufficient evidence to make separate recommendations for Aboriginal and Torres Strait Islander peoples.

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Background

Socioeconomic characteristics are well-established health determinants, affecting one's opportunities for, and access to, quality health care. Communities characterised as more socioeconomically disadvantaged, or in which health care is less accessible, tend to have shorter life expectancy and suffer from higher rates of illness, disability and death.[1]

Differences in prostate cancer diagnosis rates and outcomes have been observed for specific population groups, such as culturally and linguistically diverse communities, those from regional or rural areas, and groups with low socioeconomic status, when compared with the wider Australian population.[2] In order to reduce existing disparities, it is important to identify their needs and increase access to appropriate diagnostic and treatment programs and services.

Socioeconomic status

Several studies have demonstrated variations in prostate cancer incidence and mortality rates between men of different socioeconomic status. Between 2001 and 2005, the age-standardised incidence of prostate cancer in New South Wales was highest among men in the least disadvantaged quintile (171 per 100,000) and lowest in the most disadvantaged quintile (126 per 100,000).[3] However, prostate cancer incidence rates in the second, third and fourth quintiles were not significantly different from the New South Wales average. While differences were observed in prostate cancer incidence, age-standardised mortality rates showed no significant variations across quintiles.[3]

National cancer data obtained between 2006 and 2010 have shown that men in the least disadvantaged quintile had a higher 5-year survival rate than men in any of the other quintiles.[4] A study that used record linkage demonstrated significant differences in patterns of surgical care and all-cause mortality across the gradient of socioeconomic status in Western Australia, using the Index of Relative Socioeconomic Disadvantage (IRSD).[5] Compared with men in the least disadvantaged category, men in the most disadvantaged category were less likely to undergo radical prostatectomy (relative risk [RR] 0.63; 95% confidence interval [CI] 0.47–0.83) and had a higher all-cause mortality in the 3 years after a prostate cancer diagnosis (RR 1.34; 95% CI 1.10–1.64).5 The risk of dying within 3 years of diagnosis was also lower for men with private health insurance than for men without private health insurance (RR 0.82; 95% CI 0.76–0.89), and for men admitted to a private hospital than for those admitted to a public hospital (RR 0.77, 95% CI 0.71–0.84).[5]

Geographical factors

The Australian Bureau of Statistics Australian Standard Geographic Classification (ASGC) Remoteness Areas is one of the geographical classifications that is currently used in Australia. It allocates areas to one of five categories: major cities, inner regional, outer regional, remote and very remote.[6] More than half of Australia's outer regional, remote and very remote population reside in areas of socioeconomic disadvantage.[7] The highest age-standardised incidence rate for prostate cancer was observed in inner regional areas (186 per 100,000) compared with all other regions of Australia.[2]

From 1993 to 2007, prostate cancer mortality rates fell for men in both urban and rural areas. However, studies have continued to show a significant difference between the two.[8] [9] An Australian population-based study assessing urban-rural differences in prostate cancer testing and outcomes between 2000 and 2002 found a 21% (95% CI 14%–29%) higher age-standardised prostate cancer mortality among men living in rural areas compared with those living in capital cities. The authors hypothesised that such an excess could be related to the lower uptake of PSA testing and radical prostatectomy in rural areas.[8] Population-based data from 2001 to 2010 were analysed and showed no improvement in age-standardised prostate cancer mortality ratios for men in rural areas compared with those in metropolitan areas, from 1.17 (95% CI 1.13–1.21) in 1997–2000 to 1.18 (95% CI 1.15–1.21) in 2006–2010.[10]

Cancer registry data and hospital admission records between 1993 and 2002 were linked to determine the differences in surgical care for prostate cancer between men in urban and rural areas of New South Wales. Men from less accessible areas were more likely to undergo bilateral orchidectomy (RR 1.36; 95% CI 1.26–1.47) and less likely to have radical prostatectomy (RR 0.69; 95% CI 0.65–0.73).[11] An analysis of five-year relative survival by geographic remoteness of New South Wales found a three-fold higher relative excess risk (RER) of death from prostate cancer (RER 3.38; 95% CI 2.21–5.16) among rural residents than those in highly accessible areas.[12]

Aboriginal and Torres Strait Islander men

Aboriginal and Torres Strait Islander men in Australia are less likely to be diagnosed with prostate cancer, compared with non-Aboriginal Australian men.[13][14] Data collected from the Northern Territory Cancer Registry between 1991 and 2001 showed an incidence rate ratio of 0.2 (95% CI 0.1–0.3) for Aboriginal men compared with the whole Australian population.[15] Aboriginal men from the Northern Territory were also less likely to die from prostate cancer, indicated by a mortality rate ratio of 0.4 (95% CI 0.2–0.8).[16]

While Aboriginal men were less likely to be diagnosed with or die from prostate cancer, they have been shown to have a lower 5-year survival rate after the diagnosis of prostate cancer.[13] By linking data from the New South Wales Cancer Registry with New South Wales hospital inpatient records, Aboriginal men were found to have a 53% higher risk of death from prostate cancer in the 5 years following a diagnosis.[17]

Ethnicity and race

Analyses have shown that men born overseas have a lower age-standardised prostate cancer incidence rate, indicating a lower risk of diagnosis when compared to Australian-born men.[2] Age-standardised prostate cancer incidence was highest in Australian-born New South Wales residents (136.5 per 100,000), followed by those born in English-speaking countries (116.7 per 100,000) and in non-English speaking countries (89.0 per 100,000).[3]

Similar to age-standardised prostate cancer incidence, the age-standardised prostate cancer mortality rate was higher in Australian-born men.[2] In New South Wales, analysis of routinely collected data showed a significantly lower risk (age-adjusted) of prostate cancer deaths among East Asian and Southeast Asian migrants in their first 9 years of residence in Australia (RR 0.39; 95% CI 0.25–0.61) compared with Australian-born men. This initial lower risk of death, however, increased over time and reached that of Australian-born men by the third decade of residence in Australia.[18]

Variations in PSA testing by country of birth were reported in a cross-sectional analysis. Only men from East Asia had a significantly lower use of PSA tests than Australian-born men, while uptake of tests increased with increasing time of residence in Australia.[19]

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Summary

Prostate cancer is the second-most commonly diagnosed cancer in Australian men (after skin cancer), and is the second most common cause of cancer death in Australian men (after lung cancer). The illness and disability caused by prostate cancer also has a big effect on the lives of Australian men and their families.

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Tests for early prostate cancer in men without symptoms

The two tests that are commonly used to find prostate cancers early are a blood test to measure the level of prostate-specific antigen (PSA), and digital rectal examination (when a doctor examines the prostate by feeling it with a finger inserted in the rectum). Neither of these tests is very accurate. A man's PSA test result can be abnormal when he does not have prostate cancer, or his PSA result may be normal even though he has prostate cancer.

For men without symptoms of prostate cancer, choosing whether or not to have a test to find prostate cancer early is often a hard decision. This is because it is hard to tell whether a cancer found after having a test will spread or not, and whether it will cause problems during the man's lifetime. Thus men will need to decide whether to have their prostate removed (radical prostatectomy), or treated with radiation (radiotherapy), without knowing for sure the treatment is really necessary. Because of this uncertainty and because the treatment can cause problems getting an erection, bladder problems and bowel problems, doctors should fully explain the benefits and harms of testing, using booklets, charts or other tools designed to help men make the decision whether or not to have a test.

For those who decide to have prostate cancer tests, the general recommendation is to have a PSA blood test every 2 years from age 50 to age 69. For men whose risk of prostate cancer is higher than average (e.g. with a brother diagnosed with prostate cancer), regular testing can start earlier. PSA testing is not recommended for a man who is unlikely to live for another 7 years (e.g. a man who already has another serious illness), because PSA testing can generally only prevent deaths due to prostate cancer that would have occurred more than 7 years into the future. It is not possible to tell whether knowing he had prostate cancer, or having cancer treatment, would improve or worsen his quality of life.

Having a digital rectal examination at the same time as a PSA test does not greatly increase the chance of finding a cancer, but can result in more men having unnecessary prostate biopsies. Digital rectal examination by primary care doctors (e.g. GPs) is not recommended as a standard test for men who do not have symptoms of prostate cancer.

What happens after a PSA test?

As a general guide, men should be offered more tests if the PSA result is higher than 3.0 nanograms per millilitre (3.0 ng/mL). Usually, the test should be repeated 1–3 months later.

Different types of PSA in a man's blood ('free' PSA and 'bound' PSA) can be measured to provide more information. In some circumstances, a man's doctor should ask the pathology laboratory to measure the free-to-total PSA percentage. This includes when men have a PSA test result that remains a little above 3.0 ng/mL on repeat testing, and when men have a PSA test result that is just below 3.0 ng/mL but have a high risk of prostate cancer.

If the results of blood tests show that a man could have prostate cancer, he should be offered a core biopsy of the prostate, which involves taking samples of prostate tissue using a special needle. A total of 21–24 cores should be taken from different areas within the prostate gland.

If a man's first core biopsy does not find any prostate cancer, there is still a chance he could have prostate cancer or could develop prostate cancer. He should be offered check-ups, which usually involve regular PSA testing, and, increasingly, multiparametric magnetic resonance imaging (a type of MRI scanning that is available in some specialist centres). If these are abnormal, more biopsies may be needed.

Treatment options for prostate cancers found by PSA testing*

If prostate cancer is found on a core biopsy, a man can choose whether or not to have the cancer treated straight away. When prostate cancer grows slowly, as it quite commonly does, men may die of other causes before the prostate cancer becomes a problem. For an apparently slow growing cancer, the doctors may recommend that the man consider active surveillance instead of immediate active treatment. Choosing active surveillance could allow a man to avoid the problems that surgery or radiotherapy bring.

Active surveillance involves PSA tests every 3 months, rectal examination every 6 months, biopsies from time to time, and (in specialised centres) multiparametric MRI. If the cancer shows signs of growing, the man can have surgery or radiotherapy. In general, men with low-risk prostate cancer who choose this option instead of immediate prostate cancer treatment do not have a higher risk of dying from prostate cancer within the next 10 years. For men younger than 60 years, choosing active surveillance might just delay surgery or radiotherapy rather than avoid it.

Watchful waiting is another approach to monitoring a prostate cancer that was found as a result of PSA testing. It is mostly chosen when the cancer is already at an incurable stage, the man is unlikely to live for another seven years regardless of the prostate cancer or the man has decided not to have surgery or radiotherapy under any circumstances. Unlike active surveillance, a man on watchful waiting will generally not be offered potentially curative therapy if the cancer begins to grow. Treatment may be offered, however, to slow the growth of the cancer or to relieve symptoms. Watchful waiting involves regular PSA tests and clinic check-ups. Men with early prostate cancer who choose watchful waiting are more likely to have the cancer spread and are more likely to die of prostate cancer than if they had chosen immediate cancer treatment (e.g. radical prostatectomy or radiotherapy). On the other hand, men who choose immediate treatment are more likely to experience bladder, bowel or sexual problems than those who choose watchful waiting.

* This guideline makes recommendations about managing prostate cancers that are discovered as a result of PSA testing and follow-up. General information about prostate cancer treatments is available from Prostate Cancer Foundation of Australia.

Updating these recommendations

Medical research is constantly providing new evidence for the best ways to find and manage prostate cancer. Newly published literature relevant to each systematic review question will be monitored. If strong evidence supporting a change in the guideline accumulates, the Expert Advisory Panel will reconvene to assess if a guideline update is warranted. The guideline as a whole will be reviewed every 3 years and a decision made as to whether partial or full updating is required.

Summary of recommendations

The guidelines have been produced by a process of systematic literature review; critical appraisal and consultation encompassing all interested parties in Australia (see Appendix 1).

This guideline includes evidence-based recommendations (EBR), consensus-based recommendations (CBR) and practice points (PP) as defined in Table 4. Recommendations and practice points were developed by working party members and sub-committee members.

Each EBR was assigned a grade by the expert working group, taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence supporting each recommendation – see Table 2.

Information about levels of evidence can be found in the Evidence Summaries for each recommendation in each chapter.

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Recommendations

Risk

The question does not lead to a recommendation.

Testing

PSA Testing strategies

Recommendation	Grade
For men at average 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.	**C**

Point(s)
If the necessary data become available and the required processes put in place to ensure effective implementation, consider replacing > 3.0 ng/mL with > 95th percentile for age as the criterion for further investigation.
Do not offer PSA testing at age 40 years to predict risk of prostate cancer death.
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 at average risk of prostate cancer.
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.[iii] [iii] This Consensus-based recommendation assumes testing with the criterion for further investigation a PSA of ≥ 3 ng/mL. This recommendation will be a high priority for reconsideration when the Australian model of PSA testing has been completed. For example, use of the 95th percentile for age in place of ≥ 3 ng/mL might improve appreciably the balance of harms to benefits of testing in men 70–74 years of age.

Point(s)
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. 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. Offer testing from age 50 years according to the protocol for men who are at average risk of prostate cancer.

Role of digital rectal examination

Recommendation	Grade
In asymptomatic men interested in undergoing testing for early diagnosis of prostate cancer, digital rectal examination is not recommended as a routine addition to PSA testing in the primary care setting.	**C**

Point(s)
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.

PSA testing and life expectancy

Recommendation	Grade
Since any mortality benefit from early diagnosis of prostate cancer due to PSA	**C**

Recommendation	Grade
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.	

Point(s)

When discussing the benefits and harms of PSA testing with older men or those with a potentially fatal chronic illness, explain each of the following:

- Testing can only be expected to prevent prostate cancer death that would have occurred more than 7 years in the future.
- If prostate cancer is diagnosed after the test, medium- to long-term quality of life may be better due to diagnosis and treatment of a cancer that could have become advanced in less than 7 years.
- If prostate cancer is diagnosed after the test, quality of life in the immediate short term may be poorer due to the harmful effects of treatment.

The percentage of men of a given age, and average health status for their age who are expected to live for another 7 years is as shown in the **table below**.

(The table is provided at the bottom of this page)

Testing with variants of PSA to improve sensitivity after an initial total PSA ≤ 3.0 ng/mL

Recommendation	Grade
For men aged 45–69 years whose risk of prostate cancer is at least double the average risk and with total PSA 2.0–3.0 ng/mL, consider offering prostate biopsy if free-to-total PSA is less than 25%.	**D**

Point(s)

Do not use PSA velocity or the PHI test as adjuncts to total PSA testing in determining whether or not to offer prostate biopsy, except in the context of research conducted to assess their utility for

Point(s)
this purpose.

Testing with variants of PSA or repeat PSA testing to improve specificity after an initial total PSA > 3.0 ng/mL

Recommendation	Grade
For men aged 50–69 years with initial total PSA greater than 3.0 ng/mL, offer repeat PSA within 1–3 months. For those with initial total PSA greater than 3.0 ng/mL and up to 5.5 ng/mL, measure free-to-total PSA percentage at the same time as repeating the total PSA.	**D**
Measurement of PSA velocity is not recommended to increase specificity of a total PSA test result of 3.0 ng/mL or greater.	**D**

Point(s)
For men aged 50–69 years with initial total PSA greater than 3.0 ng/mL who have undergone repeat total PSA and free-to-total PSA percentage tests at follow-up 1–3 months later, offer prostate biopsy: + if repeat total PSA is greater than 5.5 ng/mL, regardless of free-to-total PSA percentage + if repeat total PSA is greater than 3.0 ng/mL and less than or equal to 5.5 ng/mL **and** free-to-total PSA is below 25%.
For men aged 50–69 years with a previous total PSA test result greater than 3.0 ng/mL who are not offered prostate biopsy (or do not accept prostate biopsy when offered) after follow-up PSA testing, explain that there is a small chance of missing a significant cancer and advise them to return for PSA testing within 2 years.
Do not use the PHI test to increase specificity of a total PSA test result of 3.0 ng/mL or greater, except in the context of research conducted to assess its utility for this purpose.

Decision support for men considering PSA testing

Recommendation	Grade
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.	**C**

Point(s)
Familiarity with the NHMRC fact sheet *PSA testing for prostate cancer in asymptomatic men. Information for health practitioners*, which summarises evidence on the benefits and harms of PSA testing, should help health practitioners to accurately inform men about PSA testing.

Prostate biopsy and multiparametric MRI

Biopsy quality criteria

Recommendation	Grade
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.	**B**

Point(s)
Before offering biopsy after an elevated total PSA test result, take into account a man's family history of prostate cancer (see Chapter 1 Risk) and the results of further investigations (see 2.5 Testing with variants of PSA to improve sensitivity after an initial total PSA ≤ 3.0 ng/mL and 2.6 Testing with variants of PSA or repeat PSA testing to improve specificity after an initial total PSA > 3.0 ng/mL).
Transrectal and transperineal biopsy approaches are both acceptable with respect to rates of cancer detection. The approach taken should be based on the man's wishes, the surgeon's experience, risk of sepsis and other morbidity, and practical issues such as cost and access to the necessary facilities.

Follow-up to a negative prostate biopsy

Recommendation	Grade
Advise men whose initial biopsy is negative for prostate cancer that they should continue to be followed. Monitor more closely men with abnormal findings on pre-biopsy digital rectal examination, and those whose biopsy findings included either atypical small acinar proliferation or high-grade prostatic intra-epithelial neoplasia. In addition to further PSA testing and digital rectal examination, consider prostate imaging with investigations that can help to localise the site of cancer within the prostate, and repeat biopsy using a targeted approach.	**D**
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. Do not offer another biopsy if the multiparametric MRI (using T2- and diffusion-weighted imaging) is negative, unless any of the following risk factors are present: ■ atypical small acinar proliferation on initial biopsy ■ abnormal digital rectal examination before the initial biopsy ■ high-grade prostatic intraepithelial neoplasia on initial biopsy.	**D**

Point(s)
Multiparametric MRI should be used only in centres with experienced radiologists appropriately trained in the use of multiparametric MRI to aid urologists in the management of individual patients. [iv] [iv] Refer to Urological Society of Australasia position statement: Status of mp-MRI prostate 2012: report from the MRI Prostate Working Party (available at www.usanz.org.au).
Clinicians and other staff performing multiparametric MRI should do so in accordance with appropriate standards and guidelines for its use.[v] [v] See Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. European urology 2013; 64: 544-552.
The recommendations for multiparametric MRI apply only to its use in patients who have already undergone biopsy. Primary healthcare professionals should not order multiparametric MRI in the

Point(s)
initial investigation of suspected prostate cancer in men with raised PSA levels.
Advise patients not undergoing repeat biopsy after a normal multiparametric MRI that there is a 10–15% chance of missing a significant cancer and that further follow-up is recommended.
For men at average risk for prostate cancer whose initial biopsy is negative for prostate cancer, and who have a life expectancy of less than 7 years (e.g. due to their age or due to other illness), advise that no further action is recommended unless they develop symptoms that suggest prostate cancer.

Active surveillance and watchful waiting

Active surveillance

Recommendation	Grade
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.	**C**

Point(s)
Advise men with low-risk prostate cancer that, if they choose active surveillance, their risk of death due to prostate cancer over the next 10 years would be low, and would probably be no greater than if they were to choose immediate definitive treatment.
When considering active surveillance, take into account other factors that may be associated with risk of future pathological progression but for which evidence is inconsistent (e.g. total cancer length at biopsy, tumour volume, PSA doubling time < 3 years and PSA density).
In centres where staff have skills and experience in the use of multiparametric MRI for prostate examination, consider using it to help identify foci of potentially higher-grade disease, aid targeting at reclassification biopsies and aid determination of interval tumour growth. Clinicians and other staff performing multiparametric MRI should refer to appropriate standards and guidelines for its use (Moore CM et al 2013).

Point(s)
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. For men aged less than 60 years, consider offering active surveillance based on the above criteria, provided that the man understands that treatment in these circumstances may be delayed rather than avoided.
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. If the man strongly prefers active surveillance, offer repeat biopsy to ensure that disease classification is accurate.
Consider offering definitive treatment to 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.
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.
During active surveillance, offer definitive treatment if pathological progression is detected on biopsy, or if the patient prefers to proceed to intervention.

Watchful waiting

Recommendation	Grade
For men with potentially curable prostate cancer who are considering watchful waiting, advise that: ■ the risk of developing more advanced prostate cancer and dying from it is higher with watchful waiting than with immediate definitive treatment ■ watchful waiting is unlikely to diminish wellbeing and quality of life in the medium-to-long term.	**C**

Point(s)
For men whose prostate cancer is advanced and is not curable with local treatments, follow guidelines for the management of locally advanced or metastatic prostate cancer. If no treatment is offered or accepted, monitor clinically and by PSA testing and reconsider androgen deprivation therapy if any of the following occur: + symptomatic local disease progression + symptomatic or proven metastasis + a PSA doubling time of < 3 months, based on at least three measurements over a minimum of 6 months (this should warrant consideration of further clinical investigations).

Point(s)
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.
Offer watchful waiting to men diagnosed with potentially curable prostate cancer who choose not to accept potentially curative therapy when it is offered to them.
For all men choosing watchful waiting, discuss the purpose, duration, frequency and location of follow-up with the man and, if he wishes, with his partner or carers. Source: adapted from [UK] National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. National Collaborating Centre for Cancer; 2014.

Point(s)
Specialists should consider referring men without advanced incurable prostate cancer back to their general practitioners for follow-up in primary care according to a protocol the specialist suggests and/or these guidelines. If there is no evidence of significant disease progression (as indicated by 3–4 monthly PSA levels over 1 year and absence of relevant symptoms), continue monitoring by 6-monthly PSA levels. If there is evidence of significant disease progression (that is, relevant symptoms and/or rapidly-rising PSA level), refer to a member of the treating team (urologist, medical oncologist or radiation oncologist) for review.

PSA testing and life expectancy

Age	Percentage of men remaining alive after 7 years
50	97%
55	96%
60	94%
65	91%
70	85%
75	74%
80	57%
85	37%
90	19%

TNM classification of prostate tumours

Appendix 4 TNM classification of prostate tumours

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Prostate Cancer Foundation of Australia

Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

Published: 2015

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Testing

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Prostate Cancer Foundation of Australia

Cite this guideline

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This chapter summarises evidence about strategies for prostate-specific antigen (PSA) testing as a tool for early diagnosis of prostate cancer in primary care and makes recommendations applicable to this setting. It makes no recommendations about population screening, and the recommendations in this guideline would not necessarily apply to population screening for prostate cancer using PSA as the screening test.

Developing an effective and acceptable approach for testing to detect early prostate cancer in men attending primary care who do not have symptoms that suggest they might have prostate cancer involves determining:

- whether early diagnosis and treatment of prostate cancer would be likely to benefit the patient
- which methods of decision support for men increase their capacity to make an informed decision whether to undergo PSA testing
- which strategies for PSA testing provide the best balance between the benefits and harms of testing for men without a history of prostate cancer or symptoms that might indicate prostate cancer

- how (if at all) PSA testing strategies developed for men at average risk of prostate cancer should be modified for men at high risk of prostate cancer
- which men would be unlikely to live long enough to benefit from PSA testing
- the role of digital rectal examination (DRE), if any, in association with PSA testing
- which further PSA tests (e.g. free-to-total PSA percentage, PSA velocity, Prostate Health Index) should be offered to improve the chance of detecting clinically important cancer, when the initial PSA test result is below the threshold selected as an indication for biopsy
- which further PSA tests (e.g. free-to-total PSA percentage, PSA velocity, Prostate Health Index, repeated total PSA) should be offered before referring for biopsy, when the initial PSA test result is above the threshold selected as indication for biopsy.

See also Chapter 2 Discussion.

Testing with variants of PSA or repeat PSA testing to improve specificity after an initial total PSA > 3.0 ng/mL

For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring free-to-total PSA percentage improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL? **(PICO^{i} question 6.2b)**

For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring PSA velocity improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL? **(PICO^{i} question 6.2b)**

For asymptomatic men with an initial total PSA above 3.0 ng/mL, does measuring the Prostate Health Index (PHI) improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single elevated total PSA result above 3.0 ng/mL? **(PICO^{i} question 6.3b)**

For asymptomatic men with initial total PSA above 3.0 ng/mL, does repeating the total PSA test and using an initial and repeat total PSA above 3.0 ng/mL as the indication for biopsy, improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single total PSA result above 3.0 ng/mL as the indication for biopsy? **(PICO^{i} question 6.4)**

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Contents

Background

A total PSA threshold of 4.0 ng/mL has traditionally been used as the criterion for prostate biopsy. The current trend towards the use of lower total PSA thresholds (e.g. 3.0 ng/mL), in place of 4.0 ng/mL or thresholds based on age-related normal values, has the potential to increase the number of prostate biopsies performed.

In asymptomatic men without a diagnosis of prostate cancer, a single total PSA test result above 3.0 ng/mL identifies three-to-four times as many men who do not have prostate cancer on biopsy as it does men who do have prostate cancer (positive predictive value [PPV] of 20–25%).[1] Consequently, there has been increasing interest in developing strategies to reduce the number of unnecessary biopsies as this reduces the risk of complications of biopsy, discomfort and cost. While improvements in PSA testing specificity may reduce unnecessary biopsies, ideally such strategies would not materially reduce the sensitivity of PSA testing to presence of prostate cancer. Our analysis is based on the following assumptions:

- A reduction in sensitivity of less than 10% is acceptable.
- It is desirable that, for every cancer missed, at least 3–4 unnecessary biopsies are avoided.

These systematic reviews focused on tests that improved specificity for men with a total PSA level above 3.0 ng /mL. Because of the analytical and biological variability of total PSA, including the chronological rise in PSA in men in their sixties, this review focused on studies that used total PSA thresholds between 2.0 and 4.0 ng/mL or age-specific thresholds. Restricting the evidence to studies that used a total PSA threshold of 3.0 ng/mL would have limited the evidence and would not have taken into account analytical variation in the total PSA test over the last two decades.

Men with only slightly elevated levels are less likely to have prostate cancer and could benefit from attempts to improve specificity without compromising sensitivity, whereas men with higher PSA levels are more likely to have prostate cancer and for such men attempts to reduce unnecessary biopsies could compromise the effectiveness of the recommended PSA testing strategy. As a result, studies using a single total PSA threshold were restricted to those whose participants had a total PSA ≤ 5.5 ng/mL unless there were analyses for older men (who are more likely not to have prostate cancer despite a total PSA > 5.5 ng/mL). The majority of studies that included men with total PSA levels above 3.0 ng/mL threshold also included men with levels up to 10.0 ng /mL. Accordingly, these studies were excluded unless they provided subgroup analysis for men with total PSA less than or equal to 5.5 ng/mL. However, an exception to this principle was that studies of repeat PSA were included if their focus of investigation was the threshold for repeat PSA, and the initial PSA was a lesser concern.

To reduce the potential for bias, studies were restricted to those in which all participants underwent biopsy and there were clear indications for biopsy which included a specified total PSA threshold.

Free-to-total PSA percentage

Lowering the total PSA threshold to 3.0 ng/mL (compared with 4.0 ng/mL) will result in an increase in sensitivity and a fall in specificity.[2] In principle, free-to-total PSA% can then be used to improve specificity. As the ratio of false positive to true positive biopsies with total PSA alone is typically three or four to one, a combined strategy with free-to-total PSA% should improve the efficiency of testing by removing more than three or four false positive biopsies for the loss of one true positive cancer detected.

PSA velocity

More formal analysis of PSA dynamics, such as PSA velocity, PSA doubling time or PSA change require at least three or four total PSA measurements separated by several months. For men with total PSA levels already above the threshold, the delay in obtaining these PSA dynamic parameters may cause both anxiety and the possibility that the cancer will spread during that period.

Prostate Health Index

Criteria for biopsy have been proposed based on PHI[ii] thresholds. A given PHI threshold might not be exceeded in a situation where pro2PSA is low and/or free PSA is high, despite a total PSA value greater than 3.0 ng/mL. Therefore, combining a total PSA threshold of 3.0 ng/mL with PHI might avoid unnecessary biopsies without significantly reducing the rate of detection of prostate cancer. PHI is a relatively new test and most PHI studies have been performed retrospectively. Furthermore, the ability of the PHI test to offset the decrease in total PSA specificity with increasing age is not understood.

Repeated total PSA

Given the current focus on total PSA above a given threshold as the criterion for referral or biopsy, men will often be referred as soon as total PSA is above the threshold, regardless of the possibility that such elevation may represent a transient rise from a lower baseline. Day-to-day biological variability of 15% in a man's PSA level also means that for a man with an average level of 3.0 ng/mL the levels on consecutive days can be as high as 3.9 ng/mL (upper 95th percentile) or as low as 2.1 ng/mL (lower 95th percentile). It has therefore been suggested that elevated total PSA should be confirmed by a repeat test within several weeks. Should the repeat total PSA be below the total PSA threshold, biopsy might be avoided and cancer detection unaffected.

Evidence

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Free-to-total PSA percentage

A total of 14 studies met the inclusion criteria for this systematic review.

Twelve diagnostic accuracy studies[3][4][5][6][7][8][9][10][11][12][13] were identified that compared the diagnostic performance of the free-to-total PSA% test with that of total PSA alone in men with total PSA levels above the threshold for biopsy but below 5.5 ng/mL or an age-specific threshold. All were assessed to be at risk of bias.[iii]

These studies found that lowering the free-to-total PSA% threshold gradually lowered sensitivity and improved specificity. Eight studies used a free-to-total PSA% threshold that retained a sensitivity of over 90% compared to total PSA alone.[5][6][7][9][10][11] For men with a total PSA less than 5.5 ng/mL, using free-to-total PSA% thresholds of 25–31% reduced the number of unnecessary biopsies by 3.8, 4.0, 6.0, 8.0, 9.7 or 12.5 for each cancer missed. This variation may have been due to standardisation issues with both total PSA and free-to-total PSA% during the period 1997–2006.

Older men will more often have higher total PSA levels (> 4.0 ng/mL), without the presence of prostate cancer. Two studies[14][15] examined the use of free-to-total PSA% for men aged over 69 years with a total PSA of 4.0–10.0 ng/mL. In one study,[14] a free-to-total PSA% threshold of 22% resulted in over 96% sensitivity and the avoidance of at least 32 unnecessary biopsies for each cancer missed. In the other study[15], the use of a free-to-total PSA% threshold of > 25% resulted in much lower improvement of 4.4 unnecessary biopsies avoided for each cancer missed. The cancer detection rate in this study was 44%,[15] so it is likely to represent a high-risk cohort. This may account for the reduced ratio of the unnecessary biopsies avoided to cancers missed.

The use of very low free-to-total PSA% thresholds improved specificity but compromised sensitivity to an unacceptable degree. For example, the use of free-to-total PSA < 10% as a threshold for biopsy resulted in failure to detect 70–90% of cancers in men with total PSA ranging from 2.0–4.0 ng/mL in two studies.[3][8]

PSA velocity

One diagnostic accuracy study[16] at risk of bias[iii] was identified that compared the diagnostic performance of PSA velocity with that of total PSA alone in men with total PSA levels above the threshold for biopsy but below 5.5 ng/mL. Other studies were excluded because they did not use the recommended protocols for calculating PSA velocity.

The addition of PSA velocity to total PSA did not appear to improve diagnostic performance for men with a total PSA of 2.5–4.0 ng/mL. The single included study[16] found that, for these men, the area under the receiver–operator curve for PSA velocity was significantly less than that for total PSA, which was, in turn, significantly less than that for free-to-total PSA%. Also, using a PSA velocity threshold that missed 20% of cancers (80% relative sensitivity), only approximately 27% of unnecessary biopsies (27% relative specificity) would have been avoided.[16]

Prostate Health Index

No diagnostic accuracy studies were identified that compared the diagnostic performance of PHI with that of total PSA alone in men with total PSA levels above the threshold for biopsy but below 5.5 ng/mL.

Repeated total PSA

Two diagnostic accuracy studies at risk of bias[iii] were identified that compared the diagnostic performance of repeat total PSA with that of a single total PSA alone in men with total PSA levels above the threshold for biopsy but below 5.5 ng/mL.[17][18] Both studies found that if the total PSA was lower or normalised on the second measurement, the number of negative biopsies could be reduced. The larger study[17] found that if men were not biopsied because their total PSA had normalised to < 3.0 ng/mL, 8.6% of all cancer and 4% of higher-grade

cancer would have been missed. If men did not undergo prostate biopsy because their total PSA fell by 30%, 5.9% of cancers would have been missed.[17] In this study the ratio of avoided unnecessary biopsies to missed cancers was 4.99 if prostate biopsy was restricted to men with PSA levels that did not normalise (fall to below 3.0 ng/mL) or whose total PSA levels did not drop at least 30%.[17] The smaller study[18] using age-specific PSA thresholds found that referring for biopsy only those with total PSA levels that remained elevated, missed 6.0% of cancers and avoided 3.2 unnecessary biopsies for each cancer missed.

Evidence summary and recommendations

Evidence summary	Level	References
Free-to-total PSA In populations of men without a diagnosis of prostate cancer or symptoms that suggest prostate cancer, and with total PSA levels of 3.0–4.0 ng/mL, using a free-to-total PSA threshold of 26% as an indication for biopsy missed 7.4% of cancers, with 12.5 false positives avoided per each cancer missed. In populations of men without a diagnosis of prostate cancer or symptoms that suggest prostate cancer, and total PSA levels between 2.0 and 4.0 ng/mL, using free-to-total PSA thresholds from 25% to 31% as indications for biopsy maintained a sensitivity of at least 90%, with 3.8–12.5 false positives avoided per cancer missed. In populations of men aged over 69 years without a diagnosis of prostate cancer or symptoms that suggest prostate cancer, with a total PSA of 4.0–10.0 ng/mL and a cancer detection rate of 15%, using a free-to-total PSA threshold of 22% as an indication for biopsy maintained over 90% sensitivity and avoided 32 false positives per missed cancer. There is very little evidence for whether free-to-total PSA% improves specificity in men aged under 50 years. Studies that reported free-to-total PSA% thresholds with acceptable sensitivity either did not include men under 50, or included only a small proportion.	III-2	[15], [3], [4], [5], [6], [14], [7], [8], [9], [10], [11], [12], [13]
PSA velocity In a single level III-2 study, the use of PSA velocity to increase the specificity at PSA levels in the range of 2.5–4.0 ng/mL reduced sensitivity to an unacceptable degree.	III-2	[16]
Prostate Health Index There was no evidence for whether or not PHI testing improves the specificity of PSA testing in men with an elevated PSA up to 5.5 ng/mL, compared with PSA alone.	N/A	
Repeated total PSA	III-2	[18], [17]

Evidence summary	Level	References
In men with an initial total PSA ≥ 3.0 ng/mL who underwent a second total PSA test within 1–3 months after the initial test, referring to biopsy only those men whose total PSA failed to normalise or reduce by 30% on the repeat total PSA test missed 8.6% and 5.9% of cancers, respectively, and avoided 4.99 unnecessary biopsies per cancer missed. The use of an age-specific threshold, and referring to biopsy only those whose total PSA did not normalise on repeat total PSA, missed 6% of cancers and resulted in a ratio of unnecessary biopsies to missed cancers of 3.20.		

N/A: non-applicable

Evidence-based recommendation[?]	Grade
For men aged 50–69 years with initial total PSA greater than 3.0 ng/mL, offer repeat PSA within 1–3 months. For those with initial total PSA greater than 3.0 ng/mL and up to 5.5 ng/mL, measure free-to-total PSA percentage at the same time as repeating the total PSA.	**D**

Consensus-based recommendation[?]

For men aged 50–69 years with initial total PSA greater than 3.0 ng/mL who have undergone repeat total PSA and free-to-total PSA percentage tests at follow-up 1–3 months later, offer prostate biopsy:

- if repeat total PSA is greater than 5.5 ng/mL, regardless of free-to-total PSA percentage
- if repeat total PSA is greater than 3.0 ng/mL and less than or equal to 5.5 ng/mL **and** free-to-total PSA is below 25%.

Consensus-based recommendation[?]
For men aged 50–69 years with a previous total PSA test result greater than 3.0 ng/mL who are not offered prostate biopsy (or do not accept prostate biopsy when offered) after follow-up PSA testing, explain that there is a small chance of missing a significant cancer and advise them to return for PSA testing within 2 years.

Evidence-based recommendation[?]	Grade
Measurement of PSA velocity is not recommended to increase specificity of a total PSA test result of 3.0 ng/mL or greater.	**D**

Consensus-based recommendation[?]
Do not use the PHI test to increase specificity of a total PSA test result of 3.0 ng/mL or greater, except in the context of research conducted to assess its utility for this purpose.

Health system implications

Clinical practice

Free-to-total PSA% is in common usage when total PSA levels are elevated. The free-to-total PSA% decision thresholds used are either < 10%[19] or < 25%.

Implementation of these recommendations would not require changes in the way care is currently organised.

Misuse or new safety concerns from these recommendations are not envisaged. An increase in litigation alleging malpractice is possible if the Evidence-based and Consensus-based recommendations relating to total PSA and free-to-total PSA are not followed in practice. This potential legal risk will be mitigated by robust efforts to ensure that knowledge of the guideline is disseminated to all relevant health practitioners and the development of aids that will assist them in practising according to the guideline. The Consensus-based recommendations relating to the PSA velocity and PHI tests could mitigate risk of litigation for practitioners who practice in accordance with the evidence with respect to these tests.

Resourcing

Offering a repeat total PSA test and free-to-total PSA% test if total PSA is greater than 3.0 ng/mL will increase the number of PSA estimations and reduce the number of biopsies.

The measurement of free-to-total PSA% is reimbursable in Australia and extensively used. These recommendations should increase appropriateness of existing use.

Barriers to implementation

There are no apparent barriers to the implementation of the recommendations regarding repeat total PSA tests or free-to-total PSA% tests.

Footnote

[i] Clinical questions were translated into the PICO framework: population, intervention (or exposure), comparator and outcome (see Appendix 3).

[ii] PHI is calculated using the formula: ([-2]proPSA/free PSA) × √ total PSA.

[iii] The tool for assessing risk of bias for this type of research question classified studies as being 'at risk' or 'not at risk' (see Technical report).

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Discussion

Testing with variants of PSA to improve sensitivity after an initial total PSA ≤ 3.0 ng/mL

For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring free-to-total PSA percentage improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single total PSA result below or equal to 3.0 ng/mL? **(PICO^{i} question 6.1a)**

For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring PSA velocity improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result below or equal to 3.0 ng/mL? **(PICO^{i} question 6.2a)**

For asymptomatic men with an initial total PSA below or equal to 3.0 ng/mL does measuring the Prostate Health Index (PHI) improve the detection of prostate cancer or high-grade prostate cancer without resulting in unacceptable numbers of unnecessary biopsies, when compared with a single elevated total PSA result below or equal to 3.0 ng/mL? **(PICO^{i} question 6.3a)**

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Background

For men without a diagnosis or symptoms of prostate cancer who, after being informed of the benefits and harms of testing, wish to undergo regular PSA testing, the following strategy is recommended because it is associated with reduced risk of death from prostate cancer: offer PSA testing every 2–4 years from age 50 to age 69, and offer further investigation if the PSA is greater than 3.0 ng/mL (see 2.2. PSA testing strategies).

In asymptomatic men without a diagnosis of prostate cancer, a single total PSA test result above 3.0 ng/mL fails to detect a substantial proportion of cancers.[1] There is a particular interest in detecting prostate cancer when PSA is in the range 2.0–2.9 ng/mL, as these cancers are more likely to be clinically significant than cancers found when PSA levels are below 2.0 ng/mL. Moreover, men with increased genetic risk of prostate cancer have a significantly higher risk of having prostate cancer with total PSA levels below 3.0 ng/mL.[2]

The use of a total PSA threshold of 3.0 ng/mL will not be equivalent in all circumstances because of different analytical biases between assays. Day-to-day biological variability of 15% in a man's PSA level also means that, for a man with an average level of 3.0 ng/mL, the levels on consecutive days can be as high as 3.9 ng/mL (upper 95th percentile) or as low as 2.1 ng/mL (lower 95th percentile). Therefore, we also included studies of men with total PSA levels in the broader range of 2.0 ng/mL to 4.0 ng/mL. Nevertheless, in studies that included men with total PSA levels of 2.0–4.0 ng/mL, most participants will actually have total PSA levels between 2.0 ng /mL and 3.0 ng/mL.

Free-to-total PSA percentage

PSA is a serine protease and its active form is bound by antiproteases (particularly alpha 1 anti-chymotrypsin). Bound PSA is the main form of PSA in serum. Inactive forms of PSA, such as nicked PSA and proPSA, are not bound and represent the free forms of PSA in serum. For at least two decades it has been known that men with the lowest proportion of free PSA (e.g. less than 10%) are likely to have prostate cancer. Measurement of free PSA expressed as a percentage of total PSA (free-to-total PSA%) has been used as a method of improving the predictive efficiency of PSA testing. For example, free-to-total PSA% might be used in men with total PSA below 3.0 ng/mL to improve sensitivity. The Finnish centre of the ERSPC trial found that free-to-total PSA% was a strong predictor of the later diagnosis of prostate cancer in men with a total PSA level below 3.0 ng/mL.[3]

PSA velocity and other measures of PSA kinetics

The rate of increase in serum total PSA has been identified as a risk indicator for prostate cancer.[4] PSA velocity has been defined as the absolute increase in total PSA per year, and changes of over 0.75 ng/mL/year were initially identified as representing a threshold for increased risk. Other PSA change calculations have also been proposed and applied. These include total PSA doubling time (e.g. using a doubling time less than 3 years as an indicator of increased risk) or total PSA percentage change (e.g. using a threshold of more than 25% per year as an indicator of increased risk).

The calculations of PSA kinetics including PSA velocity, PSA doubling time or PSA percentage change, are complicated by the high day-to-day variability of total PSA levels, which is generally about 15%. Therefore, a rise of 20–30% is required before the PSA level can confidently be said to have risen. The confidence in whether a PSA has risen is improved when three or four PSA levels are taken over an extended period of months, rather than days. Guidelines for PSA kinetics measurement require at least three levels measured by the same assay, with each measurement separated by at least 3 months.[5]

Prostate Health Index (PHI)

PHI testing differs from total PSA testing and free-to-total PSA% testing in identifying whether the free PSA proportion in serum contains an abnormally high component of proforms of PSA, specifically pro2PSA. The PHI is calculated as follows:

([-2]proPSA/free PSA) × √ total PSA

The threshold values for the PHI test can be reached in a situation where the proportion of free PSA present as pro2PSA is very high and the total PSA levels are low, such as when total PSA is below the 3.0 ng/mL threshold. Therefore, the use of PHI might be expected to improve the sensitivity of PSA testing.

Evidence

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Free-to-total PSA percentage

Four diagnostic accuracy studies were identified that reported the numbers of additional cancers detected and biopsies undertaken as a result of free-to-total PSA% testing of men with total PSA levels less than the threshold for biopsy.[6][7][8][9] All were assessed to be at risk of bias.[ii]

All four studies used a total PSA threshold of 4 ng/mL and found that using free-to-total PSA% at total PSA levels below the total PSA threshold detected additional cancers. However, the numbers of extra unnecessary biopsies varied depending on free-to-total PSA% threshold, the population, and the total PSA range in which the free-to-total PSA% test was used.[6][7][8][9]

In a Japanese study[6] of men aged 50–79 years, the use of a free-to-total PSA% threshold of < 12% for men with a total PSA of 2.0–4.0 ng/mL increased detection by approximately 10%, at an incremental cost of 2.1 extra unnecessary biopsies for each additional cancers diagnosed. These results were assessed to be non-generalisable to the Australian population of men who may consider prostate cancer testing, because the cancer detection rate for men with a total PSA greater than 4.0 ng/mL was 43.1%.

A Finnish study[9] conducted in a cohort of men aged 55–67 years participating in a screening trial found that the use of a free-to-total PSA% threshold of < 16% for men with a total PSA of 3.0–4.0 ng/mL increased detection by approximately 10%, at an incremental cost of 3.9 extra unnecessary biopsies for each additional cancer diagnosed. The cancer detection rate in this study was 24.5% for a total PSA threshold of 4.0 ng/mL, which was more typical of screening populations. However, this study was not directly relevant to testing protocols using a total PSA threshold of 3.0 ng/mL, as it did not seek to improve on the sensitivity at total PSA levels below 3.0 ng/mL.[9]

Another small (n = 40) study[8] showed that for men at increased risk of prostate cancer (African American, family history of prostate cancer, or *BRCA1* positive) aged 41–69 years at biopsy and with total PSA levels less than a threshold of 4 ng/mL, the use of a free-to-total PSA% threshold of less than 27%, increased cancer detection by a factor of 2.3, with one additional unnecessary biopsy for each additional cancer detected.

The other study[7] did not provide evidence as to the improvement in sensitivity.

PSA velocity

No diagnostic accuracy studies were identified that reported the numbers of additional cancers detected and biopsies undertaken as a result of measuring the PSA velocity of men with total PSA levels less than or equal to 3.0 ng/mL.

Prostate Health Index

No diagnostic accuracy studies were identified that reported the numbers of additional cancers detected and biopsies undertaken as a result of PHI testing of men with total PSA levels less than or equal to 3.0 ng/mL.

Evidence summary and recommendations

Evidence summary	Level	References
Free-to-total PSA% A study in men aged 41–69 years at high risk of prostate cancer (African American, family history of prostate cancer, or positive for BRCA1 gene), found that the use of free-to-total PSA < 27% as the criterion for biopsy in those with total PSA between 2.0 and 4.0 ng/mL, more than doubled the number of cancers detected, compared with the use of a total PSA threshold of 4.0 ng/mL alone, and resulted in approximately one extra unnecessary biopsy for each additional cancer detected.	III-2	[6], [7], [8], [9]

Evidence summary	Level	References
One study in a screening population found that the additional biopsy criterion of low free-to-total PSA (< 12%) for men with a total PSA of 2.0–4.0 ng/mL increased prostate cancer detection by approximately 10% and resulted in two extra biopsies per additional prostate cancer detected, compared with the use of a single biopsy indication of a total PSA > 4.0 ng/mL. The results of this study may not be generalisable to the Australian population, because a high cancer detection rate was observed with a total PSA threshold of 4.0 ng/mL. In a second study in a screening population the use of a free-to-total PSA% threshold of < 16% for men with a total PSA of 3.0–4.0 ng/mL increased detection by approximately 10%, at an incremental cost of 3.9 extra unnecessary biopsies for each additional cancer diagnosed. However, this study was not directly relevant as it did not seek to improve on the sensitivity at total PSA levels below 3.0 ng/mL. A third study in a screening population reported an increase in prostate cancer detection when using free-to-total PSA% as an additional indication for biopsy however the actual increase in sensitivity with the addition of the free-to-total PSA% test was not reported.		
PSA velocity There was no evidence for whether or not measuring the PSA velocity of men with a PSA less than or equal to 3.0 ng/mL improves the detection of prostate cancer, compared with PSA alone.	N/A	
Prostate Health Index There was no evidence for whether or not PHI testing men with a PSA less than or equal to 3.0 ng/mL improves the detection of prostate cancer, compared with PSA alone.	N/A	

N/A: non-applicable

Evidence-based recommendation[?]	Grade
For men aged 45–69 years whose risk of prostate cancer is at least double the average risk and with total PSA 2.0–3.0 ng/mL, consider offering prostate biopsy if free-to-total PSA is less than 25%.	**D**

Consensus-based recommendation?

Do not use PSA velocity or the PHI test as adjuncts to total PSA testing in determining whether or not to offer prostate biopsy, except in the context of research conducted to assess their utility for this purpose.

Health system implications

Clinical practice

The use of free-to-total PSA% as an adjunct to total PSA testing in high risk men with total PSA levels between 2.0–3.0 ng/L is not currently a routine approach. Misuse or new safety concerns from these recommendations are not envisaged. An increase in litigation alleging malpractice is possible if the Evidence-based recommendation is not followed in practice. This potential legal risk will be mitigated by robust efforts to ensure that knowledge of the guideline is disseminated to all relevant health practitioners and the development of aids that will assist them in practising according to the guideline. The Consensus-based recommendation could mitigate risk of litigation for practitioners who practice in accordance with the evidence with respect to PSA velocity or the PHI test.

Resourcing

Implementation of the recommendations about free-to-total PSA% tests for men at high risk of prostate cancer and total PSA levels between 2.0–3.0 ng/mL will not have any resource implications.

The free-to-total PSA% test is reimbursable in Australia and extensively used. These recommendations should increase appropriateness of existing use.

Barriers to implementation

There are no apparent barriers to the implementation of these recommendations.

Footnote

[i] Clinical questions were translated into the PICO framework: population, intervention (or exposure), comparator and outcome (see Appendix 3).

[ii] The tool for assessing risk of bias for this type of research question classified studies as being ‘at risk’ or ‘not at risk’ (see Technical report).

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Chapter 2 Testing

Discussion

Men's expectations for prostate cancer testing

It is important to note that the expectations of men's gain in life (mean months of life gained per man diagnosed) in these protocols and the comparisons between them are of the same order of magnitude as the survival times men have expressed willingness to trade off for freedom from quality-of-life impacts that may follow definitive treatment for prostate cancer. Table 2.9 extracts data from a discrete choice experiment conducted among participants in the NSW Prostate Cancer Care and Outcomes Study.[1] Men were willing to trade off survival increments of between 3.25 months (for freedom from mild fatigue) and 27.69 months (for freedom from severe urinary leakage) when symptoms were considered individually. Therefore, mean months of life gained per man diagnosed with prostate cancer provides a meaningful measure of the balance between benefits and harms.

Table 2.9. Additional months of life needed to compensate men for each persistent treatment-related adverse effect of diagnosis of prostate cancer in excess of a base case of mild loss of libido with no other problems and 12-year life expectancy

Treatment related adverse effects	Additional months of life needed to compensate
Mild fatigue	3.25
Severe impotence	4.00
Mild urinary leakage	4.22
Mild urinary blockage	4.91
Severe loss of libido	5.02
Mild bowel symptoms	6.22
Severe fatigue	13.30
Severe urinary blockage	21.96
Severe bowel symptoms	25.31

Treatment related adverse effects	Additional months of life needed to compensate
Severe urinary leakage	27.69

Source: King et al (2012)[1]

Unresolved issues

PSA testing strategies

Notwithstanding the size and logistic complexity of the five randomised controlled trials that have studied whether PSA testing reduces mortality from prostate cancer, they provide little or no evidence for the comparative performance of different strategies (or protocols) for PSA testing.[2][3][4][5][6][7][8][9][10][11] The most we have been able to conclude from them is that for men aged 50–69 years without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, PSA testing every 2–4 years and a total PSA threshold for biopsy of > 3.0 ng/mL may reduce prostate cancer mortality. There is little or no additional evidence in the randomised controlled trials that would allow us to determine whether this combination of age at testing, interval between tests and criterion for biopsy achieves the optimal balance between the benefits and harms of PSA testing.

Although the best-quality evidence (results of randomised controlled trials) supports biennial PSA testing of men aged 50–69 years, with total PSA of ≥ 3.0 ng/mL as the criterion for further investigation, one model[12] based on the ERSPC results suggests that the criterion of total PSA > 95th percentile for age may improve the balance of benefits to harms. It also suggests that the extent of the benefit and the balance of benefits to harms are similar when testing men aged 40–49 years as it is when testing men aged 50–59 years. While the apparently small additional benefit gained with beginning testing at age 40 years would probably lie with testing in the age-group 45–49, this has not be adequately assessed in the models.

While these guidelines have recommended against PSA testing at age 40 years as a means of estimating future risk of prostate cancer death, it is nonetheless true that the PSA level when measured in the forties or early fifties is a strong predictor of risk. It has been suggested, in this context, that a man's future screening protocol could be modified in light of the first PSA test result. For example, the Royal College of Pathologists of Australia's (RCPA's) position statement *Prostate specific antigen testing: age-related interpretation in early prostate cancer detection*[13] has recommended that 'If the PSA level is not above the age-related median, the patient should be reassured that their risk is low and be re-tested in 4 years' (not 2 years as in the protocol recommended in this guideline and RCPA's recommendation for men with a PSA above the age-related median). Such tailoring of the testing protocol to risk as assessed by PSA level has the potential to appreciably reduce the harms of PSA testing while preserving the benefits and would justify early consideration using a PSA testing model developed specifically for Australian men.

Quality-of-life outcomes have not been reported to any material extent in the randomised controlled trials designed to evaluate PSA testing. Observational quality of life studies suggest that persisting consequences of definitive therapy, such as urinary incontinence, impaired sexual function, bowel problems are the most

common quality-of-life issues that men diagnosed with prostate cancer experience.[14] In principle, these can be reduced if over-diagnosis can be reduced. The broader impairment of quality of life due to androgen deprivation therapy and advanced cancer is also important and, in principle, both can be reduced by earlier diagnosis of cancers that would go on to become symptomatic in the absence of measures that achieve earlier diagnosis, such as PSA testing. The modelling studies addressed outcomes relevant to quality of life only indirectly, by estimating rates of over-diagnosis and false positives on biopsy. There would be value in extending this modelling to include a more comprehensive assessment of quality-of-life issues, as it is unlikely that they will ever be adequately addressed by randomised controlled trials.

Australian population PSA reference data

Data from modelling studies suggest that the use of an age-based PSA test criterion for biopsy may reduce rates of false positive tests and over-diagnoses, and achieve a better balance of benefits to harms than a fixed value criterion (e.g. > 3.0 ng/mL). As PSA testing models based on Australian data become available within the next 5 years, these recommendations may be revised to specify more widely biopsy criteria based on percentiles of total PSA, most likely the 95th percentile for age.

Recommendations based on total PSA percentiles for age would require data for each year of age, or for age brackets not wider than 5 years. Laboratories should routinely report these data for PSA tests on men without a prostate cancer diagnosis or symptoms that might indicate prostate cancer. There should be a single, authoritative Australian source of data on the distributions of PSA concentration in suitable age categories in Australian men.

PSA modalities for improving sensitivity and specificity

It is uncertain how repeat total PSA and free-to-total PSA% work together in avoiding unnecessary biopsies while maintaining sensitivity. Furthermore it is not known how these diagnostic changes impact on clinical outcomes. To the extent possible, their impact on overall outcome for men having PSA testing should be evaluated in the proposed Australian model for PSA testing.

The present evidence allows two discrete recommendations when initial total PSA is greater than 3.0 ng/mL in men aged 50–69 years:

- Measure free-to-total PSA% if initial total PSA is greater than 3.0 ng/mL and up to 5.5 ng/mL. If free-to-total PSA is less than 25%, offer prostate biopsy.
- Offer repeat PSA within 1– 3 months. If repeat total PSA is greater than 3.0 ng/mL, offer prostate biopsy.

However, the evidence does not indicate how these could be integrated into a practical recommendation or sequence of steps that could be implemented in clinical practice, given that a patient may meet one or both of the independent criteria for biopsy. Evidence was not available from any studies that used a clinical algorithm based on both these parameters. The use of ‘either total PSA greater than 3.0 ng/mL or free-to-total PSA% less than 25%’ as the criterion for biopsy may result in the loss of specificity gains achieved by using these tests individually. Logic and the findings of modelling studies (see **2.2 PSA testing strategies**) suggest that it would be more reasonable to reserve biopsy for those who meet both criteria, acknowledging that this more stringent threshold could reduce sensitivity.

Clinical considerations are also relevant to guidance based on this body of evidence. The result of a free-to-total PSA% measured at the time of an initial slightly elevated total PSA could be misleading (e.g. if the PSA was raised due to prostatitis, this may also affect PSA fractions). Therefore, it seems reasonable to consider the result of a free-to-total PSA% test performed after an interval of 1–3 months. In practice, clinicians request measurement of free-to-total PSA% at the same time as repeat total PSA.

In consideration of all these factors, the Expert Advisory Panel elected to make an evidence-based recommendation on the timing and choice of these tests, and to make a consensus-based recommendation on how their results should be interpreted.

Studies currently underway

Several of the prospective studies evaluating PSA testing strategies are still underway. Longer-term follow-up data may influence future recommendations.

Modelling of PSA testing protocols in the Australian context is also underway. When available, the data may enable better prediction of outcomes for Australian men and subgroups, and may result in revision of the recommendations.

Prostate Cancer Foundation of Australia has commissioned researchers at the Australian National University to develop a tool for estimating life expectancy in men using Australian data. When available, this tool would provide doctors with much of the information needed to discourage offers of PSA testing to men with less than 7 years' life expectancy.

Future research priorities

Future research priories include:

- effects of PSA testing strategies (using different combination of age at testing, interval between tests, and criterion for biopsy) on outcomes of prostate cancer-specific mortality outcomes, disease- and treatment-related morbidity, and quality of life
- Australian population reference data to establish PSA normal values for various age groups
- the interaction between multiple PSA testing modalities (e.g. PHI, repeat total PSA and free-to-total PSA%) used in conjunction with a total PSA threshold of 3.0 ng/mL, especially for men aged 50–69 years and those at high risk
- more research-based information on the RR of prostate cancer conferred by different risk factors is needed to be able to determine, with confidence, the age at which a man with one or more risk factors should consider beginning PSA testing. Currently, even for family history (probably the best known risk factor) there is considerable uncertainty in the estimates of RR, particularly with different degrees of family history (see Chapter 1 Risk). It will be important that potential confounding with PSA testing is taken into account in studies done to fill this information gap.

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Watchful waiting

For men with biopsy-diagnosed prostate cancer, for which patients (based on diagnostic, clinical and other criteria) does watchful waiting achieve equivalent or better outcomes in terms of length and quality of life than definitive treatment? (PICO question[i] 11)

For men with biopsy-diagnosed prostate cancer following a watchful waiting 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? (PICO question 12)

Conservative strategies for managing prostate cancer are considered when cure is not the goal. A comprehensive approach to managing prostate cancer diagnosed by biopsy after prostate-specific antigen (PSA) testing therefore involves determining:

- appropriate criteria for choosing watchful waiting in preference to definitive treatment
- the optimal monitoring protocol for watchful waiting, including criteria for intervention.

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Background

Watchful waiting[ii] is a conservative strategy for managing prostate cancer that is asymptomatic or for which the man declines 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. Treatment, when given, is directed towards slowing the disease's progression or relieving its symptoms, not to cure.

The decision to undertake watchful waiting is made in agreement with the patient after explaining the available options and discussing their benefits and harms. Reasons for undertaking watchful waiting include the following:

- The cancer has advanced and is not curable with local treatments.
- The patient's life expectancy is limited and prostate cancer is unlikely to cause significant problems in his lifetime.
- The patient chooses this option – some men may elect to undertake a program of watchful waiting rather than proceed with any of the localised disease management options with curative intent.

Available evidence for the outcomes of watchful waiting, compared with immediate definitive treatment, is from studies that commenced 20–25 years ago and included men with early-stage cancer and a life expectancy of more than 10 years. This group may not now be considered for watchful waiting (except at their choice). Therefore, the outcomes of these trials may not be generalisable to the population of men who would be likely to be offered watchful waiting under present circumstances. The evidence is, however, directly relevant to men with early-stage cancer and a life expectancy of more than 10 years who choose not to have definitive treatment. The outcomes of watchful waiting reported in this body of evidence could also apply to men who have early-stage cancer and a life expectancy of less than 10 years (for reasons other than prostate cancer).

Evidence about the optimal components and frequency of the clinical assessments is lacking. In patients undergoing watchful waiting, clinical assessment is designed to detect symptoms, signs and laboratory tests indicative of progressive prostate cancer that may require treatment. Physical assessment may include a digital rectal examination of the prostate to assess its local extent and progression. Laboratory testing may include serum PSA to assess the rate of progression, serum creatinine to assess renal function, serum alkaline phosphatase to help indicate the likelihood of bone metastases, and a full blood count to assess marrow involvement. Imaging studies may include radionuclide bone scans and computed tomography.

Evidence

Criteria for selecting watchful waiting

Two randomised controlled trials[1][2] were identified that reported prostate cancer-specific mortality rate and other relevant outcomes in men with early-stage (T1–2NxM0) prostate cancer randomised to immediate radical prostatectomy or to watchful waiting. Both studies were assessed to have a moderate risk of bias for the outcomes of mortality and development of distant metastases, and a high risk of bias for the outcomes of quality of life and adverse events. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

The first, Scandinavian Prostate Cancer Group trial number 4 (SPCG-4),[1] randomised 695 men with early-stage, low-grade or intermediate-grade prostate cancer, diagnosed in Sweden from 1989 to 1999, to immediate radical prostatectomy or to watchful waiting. Of men randomised to radical prostatectomy, 84.7% had radical prostatectomy and of those randomised to watchful waiting, 13.2% had definitive treatment. Intention-to-treat analysis at median 12.8 years' follow-up favoured radical prostatectomy for the following outcomes:

- all-cause mortality (hazard ratio [HR] 0.75; confidence interval [CI] 0.61–0.92)
- prostate cancer-specific mortality (relative risk [RR] 0.62; CI 0.44–0.87)
- development of distant metastases (RR 0.59; CI 0.45–0.79).

Results were also analysed in strata of age at diagnosis and risk of a poor cancer outcome (low risk defined as PSA < 10 ng/mL and either Gleason score < 7 or World Health Organization [WHO] cancer grade 1). The impact of radical prostatectomy appeared to be limited to, or greater for, men younger than 65 years for all-cause mortality (RR 0.52, compared with RR 0.98 for men older than 65 years), prostate cancer-specific mortality (RR 0.49, compared with RR 0.83 for men older than 65 years), and development of distant metastases (RR 0.47, compared with RR 0.77 for men older than 65 years). The impact of radical prostatectomy also appeared to be greater in men with low-risk cancer for all-cause mortality (RR 0.62), prostate cancer-specific mortality (RR 0.53) and distant metastases (RR 0.43). Results for the subgroup with high-risk cancer were not reported.

While limited to men with well-differentiated or moderately differentiated prostate cancer, this trial appears to have included men with more advanced primary prostate cancer than is usual at diagnosis today:

- It largely excluded patients whose prostate cancer had been detected as a result of PSA testing; only 12% had disease primarily detected by a PSA test (stage T1c).
- Biopsy techniques used (which included aspiration cytology) were less sensitive than those used at present.
- It included men with PSA levels of up to 50 ng/mL.

The second trial, Prostate Cancer Intervention Versus Observation Trial (PIVOT),[2] randomised 731 men with early-stage prostate cancer of any grade, diagnosed in the USA between 1994 and 2002, to immediate radical prostatectomy or to watchful waiting. This trial had difficulty recruiting and was underpowered. Just over 30% of participants were Black Americans. Of men randomised to radical prostatectomy, 77.2% had radical prostatectomy and 85.4% had definitive treatment. Of those randomised to watchful waiting, 10.1% had radical prostatectomy and 20.4% had definitive treatment.

Intention-to-treat analysis at median 10.0 years of follow-up favoured radical prostatectomy for development of bony metastases (HR 0.40; CI 0.22–0.70) and showed statistically non-significant trends in favour of radical prostatectomy for all-cause mortality (HR 0.88; CI 0.71–1.08) and prostate cancer-specific mortality (HR 0.63; CI 0.36–1.09).

Results were also analysed in strata of age at diagnosis, race, comorbidity, performance status, PSA level, Gleason score, and tumour risk (based on PSA, stage and biopsy findings). The impact of radical prostatectomy appeared to be limited to, or greater for, men with PSA > 10 ng/mL for all-cause mortality (HR 0.67, compared with 1.03 for PSA ≤ 10 ng/mL), prostate cancer-specific mortality (HR 0.36, compared with 0.92 for PSA ≤ 10 ng /mL), and bony metastases (HR 0.28, compared with 0.58 for PSA ≤ 10 ng/mL). The impact of radical prostatectomy also appeared to be limited to, or greater in, men with high- or intermediate-risk disease, but this effect may have been due to the inclusion of PSA in the risk algorithm, since there was little difference in radical prostatectomy effect between subgroups with Gleason score categories (< 7, > 7). However, there were differences between histological reporting at participating sites and by a central pathologist that affected risk stratification and, consequently, secondary endpoint results. Using a less predictive pre-2005 International Society of Urological Pathology Consensus Gleason classification, about 25% of patients had Gleason score of 7 or higher reported at the peripheral sites, compared with 48% with Gleason score 7 or higher by a central pathologist.

There was also little evidence that the effect of radical prostatectomy differed by age at diagnosis or any other stratification variable, but competing mortalities exacted a significant toll; 47% of men assigned to prostatectomy died, yet only 5.8% deaths were attributed to prostate cancer. Similarly, 49.9% of men assigned to observation died, yet only 8.4% deaths were attributed to prostate cancer.

Notably, only 10% of participants were younger than 60 years, compared with 20% of men diagnosed with prostate cancer in Australia in 2008. This study was begun in the 'early PSA era', but approximately 50% of men had non-palpable cancers.

These two studies are consistent in their evidence that, in men with early-stage prostate cancer, there are higher rates of all-cause mortality, prostate cancer-specific mortality, and development of distant metastases in men randomised to watchful waiting than in men randomised to radical prostatectomy. However, the studies were not consistent in the strata of personal and disease characteristics in which apparently beneficial effects of radical prostatectomy were observed. Whereas SPCG-4 observed an apparently greater reduction in rates of all-cause mortality, prostate cancer-specific mortality, and development of distant metastases in men with low-risk cancer (PSA < 10 ng/mL and either Gleason score < 7 or WHO cancer grade 1) randomised to radical prostatectomy, PIVOT observed an apparently greater reduction in all three of these outcomes in men with a PSA > 10 ng/mL randomised to radical prostatectomy. In addition, these benefits appeared greater in younger men in SPCG-4 but unrelated to age in PIVOT.

These two studies also reported quality-of-life outcomes. In both SPCG-4[3] (at mean of 4.1 years and median of 12.2 years[4] after randomisation) and PIVOT (approximately 2 years[2] after randomisation), there were significantly greater prevalence rates of urinary incontinence, erectile dysfunction and associated distress in men randomised to radical prostatectomy than in men randomised to watchful waiting. In PIVOT, prevalence of bowel dysfunction was not different between the randomised groups at approximately 2 years after randomisation.[2] In SPCG-4, anxiety, depression, wellbeing and patient assessed quality of life were similar between the two groups at 4.1 years (mean)[3] and 12.2 years (median)[4] after randomisation. These studies provide consistent evidence of greater rates of urinary incontinence and associated distress, and erectile dysfunction and associated distress, in men randomised to radical prostatectomy than in men randomised to watchful waiting – at least up to a mean of 4 years after randomisation. Modification of these effects of treatment type by patient or disease characteristics was not examined.

PIVOT reported on adverse events occurring within 30 days of surgery. Based on cumulative incidences for 280 patients, early procedure-related adverse events included wound infection (4.3%) urinary tract infection (2.5%), requirement for additional surgical repair other than bowel repair (2.5%), bleeding requiring transfusion (2.1%), urinary catheter present at > 30 days (2.1%), bowel injury requiring repair (1.1%), and one death (0.4%).[2]

No studies were identified that compared watchful waiting with definitive treatment in men with advanced prostate cancer.

Watchful waiting protocols

No randomised controlled trials were found that tested or compared follow-up schedules or strategies for watchful waiting. In the absence of direct evidence, a useful starting point could be the schedules used for the control groups in randomised clinical trials comparing various active treatments with watchful waiting in three different clinical scenarios: locoregional prostate cancer detected by screening, locoregional prostate cancer

detected clinically, and advanced prostate cancer with minimal symptoms.[1][2][4][3][5][6][7] The components and frequency of these schedules were carefully specified for these trials, but they were designed primarily to satisfy the needs of research rather than those of routine clinical practice and may, therefore, be more intensive than would be desirable for clinical practice, both with respect to frequency and number and nature of investigations.

In the absence of relevant published evidence on which to base watchful waiting protocols, we adapted selected NICE 2014[8] recommendations, which were informed by available evidence and represent current international expert consensus.

Evidence summary and recommendations

Evidence summary	Level	References
The studies were inconsistent in patient selection and in their findings on the effects of age and risk of cancer progression (as assessed at diagnosis) on observed differences in rates of all-cause mortality, prostate cancer-specific mortality and prostate cancer metastases, between men offered radical prostatectomy and men offered watchful waiting. In the one study that reported on race, comorbidity and performance status, these factors were not associated with differences in clinical outcomes between treatment groups.	II	[1], [2]
In men with early-stage prostate cancer of any grade, watchful waiting was associated with higher rates of distant metastases and death due to prostate cancer, compared with radical prostatectomy. However, watchful waiting was associated with lower rates of erectile dysfunction, urinary incontinence and distress than radical prostatectomy. Despite these differences, rates of anxiety and depression, wellbeing, and patient-assessed quality of life did not differ between men who receive watchful waiting and those who receive radical prostatectomy, according to data from follow-up of 4.1 years (mean) and 12.2 years (median) from diagnosis.	II	[1], [4], [3], [2]
No studies were found that directly compared different watchful waiting protocols.	N/A	

N/A: non-applicable

Evidence-based recommendation?	Grade
	C

For men with potentially curable prostate cancer who are considering watchful waiting, advise that:

- the risk of developing more advanced prostate cancer and dying from it is higher with watchful waiting than with immediate definitive treatment
- watchful waiting is unlikely to diminish wellbeing and quality of life in the medium-to-long term.

Consensus-based recommendation[?]

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.

Consensus-based recommendation[?]

Offer watchful waiting to men diagnosed with potentially curable prostate cancer who choose not to accept potentially curative therapy when it is offered to them.

Consensus-based recommendation[?]

For all men choosing watchful waiting, discuss the purpose, duration, frequency and location of follow-up with the man and, if he wishes, with his partner or carers.

Source: adapted from [UK] National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. National Collaborating Centre for Cancer; 2014.

Consensus-based recommendation

Specialists should consider referring men without advanced incurable prostate cancer back to their general practitioners for follow-up in primary care according to a protocol the specialist suggests and/or these guidelines.

If there is no evidence of significant disease progression (as indicated by 3–4 monthly PSA levels over 1 year and absence of relevant symptoms), continue monitoring by 6-monthly PSA levels.

If there is evidence of significant disease progression (that is, relevant symptoms and/or rapidly-rising PSA level), refer to a member of the treating team (urologist, medical oncologist or radiation oncologist) for review.

Practice point

For men whose prostate cancer is advanced and is not curable with local treatments, follow guidelines for the management of locally advanced or metastatic prostate cancer. If no treatment is offered or accepted, monitor clinically and by PSA testing and reconsider androgen deprivation therapy if any of the following occur:

- symptomatic local disease progression
- symptomatic or proven metastasis
- a PSA doubling time of < 3 months, based on at least three measurements over a minimum of 6 months (this should warrant consideration of further clinical investigations).

Health system implications

Clinical practice

Implementation of this recommendation would not require any changes in the way care is currently organised.

Resourcing

Implementation of this recommendation would have no significant implications for resourcing.

Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

Discussion

Footnotes

[i] Clinical questions were translated into the PICO framework: population, intervention, comparator and outcome (see Appendix 3).

[ii] Watchful waiting is another approach to monitoring a prostate cancer that was found as a result of PSA testing. It is mostly chosen when the cancer is already at an incurable stage, the man is unlikely to live for another seven years regardless of the prostate cancer or the man has decided not to have surgery or radiotherapy under any circumstances. Unlike active surveillance, a man on watchful waiting will generally not be offered potentially curative therapy if the cancer begins to grow. Treatment may be offered, however, to slow the growth of the cancer or to relieve symptoms. Watchful waiting involves regular PSA tests and clinic check-ups. Men with early prostate cancer who choose watchful waiting are more likely to have the cancer spread and are more likely to die of prostate cancer than if they had chosen immediate cancer treatment (e.g. radical prostatectomy or radiotherapy). On the other hand, men who choose immediate treatment are more likely to experience bladder, bowel or sexual problems than those who choose watchful waiting.

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Supporting attachments

Discussion

Guidelines developed in partnership with

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Cite this guideline

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

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Contents

Chapter 5 Watchful waiting

Discussion

Unresolved issues

The optimal criteria for choosing watchful waiting have not been identified.

Emerging research may provide more information on the relative contribution of prostate cancer and other illness to cause of death among men undergoing watchful waiting.

Further follow-up data from SPCG-4 (see 5.1 Criteria for selecting watchful waiting) were published after the systematic reviews were completed for this guideline. The investigators reported that 200 of the 347 men in the radical prostatectomy group and 247 of the 348 in the watchful waiting group died during median of 13.4 years follow-up. Death was due to prostate cancer in 99 men assigned to watchful waiting and 63 men assigned to radical prostatectomy ($p = 0.001$).[1]

There is no high-quality evidence on which to base protocols for watchful waiting.

Studies currently underway

The SPCG-4[1] and PIVOT[2] studies are currently underway.

Future research priorities

Important unresolved questions for men with prostate cancer being managed with watchful waiting include:

- whether there are unmet needs and, if so, their rates and significance
- the optimal triggers and timing for starting anticancer treatment
- the optimal components and frequency of follow-up.

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