Clinical practice guidelines for PSA testing and early management of test-detected prostate cancer

Prostate Cancer Foundation of Australia and Cancer
Council Australia are currently developing clinical
practice guidelines for PSA testing and management of test-detected prostate cancer. The draft guidelines are going to be launched for public consultation on 4 December 2014.

The draft documents as well as public consultation information will be available from this website.

UPLOAD IN PROGRESS

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1 Foreword

Very many Australians are concerned about prostate cancer. Rightly so, because every year almost 20,000 Australian men are diagnosed with the disease and 3,300 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. Thus, we cannot afford – as suggested by the old adage "prostate cancer is a disease old men die with, not of" – to ignore this important health issue. It touches the lives of too many Australian men and their families.

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Whilst there is common agreement amongst health professional bodies that there is currently insufficient evidence to support a population-based PSA screening program for prostate cancer, there is a lack of consensus on what advice to offer a man who requests a PSA test or his doctor. This causes widespread confusion for men and their health advisers. Notwithstanding the confusion, each year about 20% of Australian men aged 45 to 74 have a PSA test, which is not dissimilar to the participation rate of eligible women in the BreastScreen Australia program.

This guideline is intended for use in this context; that is, interactions between men and their doctors in which a man might request a PSA test or his doctor might offer one. They do not propose a national PSA screening program. The recommendations are intended to bring order to the present situation and to ensure that men and their doctors are able to make informed choices based on the latest available evidence. They were developed by a broad-based Expert Advisory Panel which included general practitioners, public health experts, urologists, pathologists, radiation oncologists, allied health professionals and consumer representatives, and the guideline is supported by Prostate Cancer Foundation of Australia and Cancer Council Australia.

The guideline provides clear, consistent, evidence-based guidance on PSA testing and early management of test-detected prostate cancer and I commend it to you.

2 Preface

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

Measurement of Prostatic 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 isn't perfect either and its assessment requires a prostate biopsy. 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.

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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 the 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

3 Summary

This guideline contains recommendations for prostate cancer testing in men without known prostate cancer or symptoms of prostate cancer, and for managing early prostate cancer in men who have been diagnosed with the disease after a blood test to measure prostate specific antigen (PSA).

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7 Updating these recommendations

3.1 About prostate cancer

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). It also affects Australian men's lives by causing illness and disability.

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. Men with prostate cancer from socioeconomically disadvantaged areas have lower medium-term survival rates than the least disadvantaged. Compared with the average for all Australian men, Aboriginal and Torres Strait Islander men are less likely to be diagnosed with prostate cancer, but more likely to die of prostate cancer.

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3.2 Tests for early prostate cancer

The main aim of early diagnosis of prostate cancer is to reduce the risk of death from prostate cancer. An ideal test would enable doctors to diagnosis prostate cancer before it causes symptoms, and early enough for a high chance of cure.

The two tests that are commonly used to find prostate cancers early are the PSA blood test and digital rectal examination (when a doctor examines the prostate by feeling it with a finger inserted in the rectum). Both these tests can currently identify men who may have prostate cancer, but they are not very accurate. The amount of PSA in blood can be raised even when the man does not have cancer, or the PSA result may be normal even though the man has prostate cancer.

If the result of a PSA test or digital rectal examination show that a man may have prostate cancer, the next step is usually biopsy of the prostate. This involves taking samples of prostate tissue using a special needle (core biopsy) in the doctor's office or in hospital under general anaesthesia. The samples are examined under the microscope by a pathology laboratory.

Even if cancer is found after core biopsy, it is not always possible to tell whether the cancer will spread or not, and whether it is likely to cause problems during the man's lifetime. This means some men will need to choose whether to have their prostate removed (radical prostatectomy) or partially removed without being able to be completely sure if this is necessary. Unnecessary cancer treatment would not matter if surgery or other treatment options were harmless. However, prostate cancer treatments can cause bowel and bladder problems and problems getting an erection.

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3.3 Who may benefit from a PSA test?

There is no perfect test for early prostate cancer, so it is difficult for men to choose whether or not to have a PSA test. Doctors should fully explain the risks and possible benefits. They should use materials designed to help men make this decision (e.g. booklets, charts, computer programs or internet). These decision aids can improve men's knowledge about how testing may or may not help them, reduce their distress in making the decision, and improve their satisfaction with their decision.

For men aged 50–69 years without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, the risk of dying from prostate cancer can be reduced by having regular PSA testing and a core biopsy if the test is positive. If men in this age group decide to have PSA testing, after the possible risks and benefits have been explained to them, a test every 2 years is recommended, and a core biopsy is recommended if the PSA is above 3.0 nanograms per millilitre. For men with a higher risk of prostate cancer (e.g. a strong family history of prostate cancer), it may be better to start regular testing earlier. There is not enough evidence from medical research in men aged over 70 years to judge whether these men may benefit from testing or not.

Men who are unlikely to live another 7 years (e.g. because they are elderly, or already have another illness) should not be offered a PSA test, because the chance of having unnecessary medical procedures is probably greater than the chance of avoiding death from prostate cancer.

Doing 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 core biopsies when they do not have cancer. Digital rectal examination is no longer recommended as a routine test by primary care doctors (e.g. GPs) for men who do not have symptoms of prostate cancer.

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3.4 What happens after a PSA test?

Men whose PSA test is higher than normal should also be offered a repeat test. Different types of PSA in a man's blood ('free' PSA and 'bound' PSA) can be measured to provide more information, and changes in a man's PSA result over time can also be analysed in different ways. In some circumstances, a man's doctor should ask the pathology laboratory to measure the ratio of free PSA to total PSA in the blood sample (free-to-total PSA). This includes men whose PSA test result is only a little higher than normal, and men whose PSA test result is 'normal' but have a high risk of prostate cancer (e.g. those with a strong family history of prostate cancer).

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3.5 Core biopsy and imaging

When the result of a man's PSA tests suggest the possibility that he has prostate cancer, he should be offered a core biopsy. A total of between 21 and 24 cores should be taken from different areas within the prostate. Taking 24 cores increases the chance of finding prostate cancer, compared with 12 or 6 cores, which were the usual numbers in the past.

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If a man's first core biopsy does not find any prostate cancer, there is still a chance he could have prostate cancer or develop prostate cancer. He should consider having check-ups, which usually involves regular PSA testing and digital rectal examination. Follow-up is especially important if the biopsy showed abnormalities, even if cancer itself was not found.

If prostate cancer is suspected (e.g. because symptoms develop or the prostate feels abnormal on digital rectal examination), imaging tests should be considered to find which area of the prostate looks abnormal. Imaging can include multiparametric magnetic resonance imaging (a specialised type of MRI that is available in some specialist centres).

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3.6 Treatment options for prostate cancer

This guideline does not make recommendations about all aspects of prostate cancer treatment, but only about prostate cancers found by PSA testing in men without symptoms.

If prostate cancer is found on a core biopsy, this does not mean that it is a life-threatening cancer. When prostate cancer grows slowly, men may die of other causes before the prostate cancer becomes a problem. Each man and his doctors need to decide which is the best choice for him, depending on the type of prostate cancer and his own general health and age. The choices can include having the prostate surgically removed (radical prostatectomy) or regular check-ups to see whether the cancer is changing. Check-ups usually involve regular PSA tests, digital rectal examination, and regular core biopsies.

The after effects of radical prostatectomy can include bowel, bladder and sexual problems. When doctors consider that there is only a low risk that the prostate cancer will become a problem, men may choose to avoid prostatectomy.

'Active surveillance' is a method of monitoring low-risk prostate cancer in men who have chosen not to have immediate radical prostatectomy. It involves PSA tests every 3 months, rectal examination every 6 months, a series of biopsies, and (in specialised centres) multiparametric MRI. If the cancer grows, the man can undergo radical prostatectomy. In general, men who choose this option do not have a higher risk of dying from prostate cancer, provided their prostate cancer has features that mean it is probably low risk (PSA no higher than 20 ng /dL, clinical stage T1-2, and Gleason score no higher than 6). For younger men, choosing active surveillance may only delay radical prostatectomy but not avoid it.

'Watchful waiting' is another method of monitoring low-risk prostate cancer that is not causing symptoms. Unlike active surveillance, watchful waiting does not aim to cure prostate cancer, but only to slow the growth of the cancer or relieve symptoms if necessary. It involves regular PSA tests and clinic check-ups. Cancer treatment (e.g. hormonal manipulation) can be considered if the cancer is spreading and producing symptoms. Cancer treatment (e.g. hormonal treatment, removal of the testicles, or radical prostatectomy) can be reconsidered if the cancer grows or spreads.

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Some men choose watchful waiting instead of immediate cancer treatment if the cancer is already incurable, or if they are more likely to die of another cause before prostate cancer becomes advanced (e.g. men a life expectancy of less than 7 years). Men with early prostate cancer who choose watchful waiting are more likely to have the cancer spread and more likely to die of prostate cancer than if they had chosen immediate cancer treatment. On the other hand, men who choose radical prostatectomy are more likely to experience bladder, bowel or sexual problems than those who choose watchful waiting.

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3.7 Updating these recommendations

Medical research is constantly discovering more evidence on the best way to deal with prostate cancer. The recommendations in this guideline may be revised over the next few years (see Appendix 1).

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4 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 i. 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 ii.

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

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4.1 Recommendations

4.1.1 Risk

The question does not lead to a recommendation.

4.1.2 Testing

4.1.3 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.

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Point(s)
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.
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.

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4.1.4 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

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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.

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4.1.5 PSA testing and life expectancy

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

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**.

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4.1.6 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 this purpose.

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4.1.7 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

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Point(s)
⁺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.

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4.1.8 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.

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4.1.9 Prostate biopsy and multiparametric MRI

4.1.10 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	**B**

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Recommendation	Grade
prostate.	

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.

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4.1.11 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 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.

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4.1.12 Active surveillance and watchful waiting

4.1.13 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**

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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

Point(s)
✠ 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.

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4.1.14 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

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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.

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.

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Note: Please submit your comments on the individual recommendations and practice points on the content pages.

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5.1 Prostate cancer in Australia

Prostate cancer is an important public health issue. It is the most commonly diagnosed cancer in Australian men (skin cancer excepted).[1] Over the most recent decade of reports on cancer incidence in Australia, prostate cancer diagnoses nearly doubled from 10,942 in 2000 to 19,821 in 2010.[1] In 2010, 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 3294 men died from prostate cancer in 2011.[1] That represents 4.7% of all deaths in men and 13.4% 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).[3]

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5.2 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, about seven Australian men younger than 50 years of age die from prostate cancer. From a rate of about 1 death per year per 100,000 men 45–49 years of age, mortality rate in Australia increases 2–4 fold with each five years increase in age to a maximum of about 800 deaths per year per 100,000 men aged 85 years and over.

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. While available data are limited, mortality appears also to be high in African countries, and African American men are also at high risk of death from prostate cancer.[4][5]

Within Australia, the mortality rate from prostate cancer is 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. In addition, it is highest among men of lowest socioeconomic status, and becomes progressively higher with increasing remoteness of a man's place of residence.

Available evidence indicates that mortality from prostate cancer in Australian Aboriginal men is higher than in other Australian men but that incidence is lower. 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.

A family history of prostate cancer, especially having a male first-degree relative diagnosed with prostate cancer before age 65 years,[6] increases a man's risk of developing it. The *BRCA1* and *BRCA2* gene mutations, which are associated with a high risk of breast cancer, are the mutations best known to increase risk for prostate cancer. 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 none with sufficient certainty or strength of association to be a target for risk reduction.

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5.3 Testing for the early diagnosis of prostate cancer

5.3.1 Efficacy of testing

This guideline informs testing for the early diagnosis of prostate cancer in men who are of an age when prostate cancer is likely to occur or 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 offered or requested 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 prostate specific antigen (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 mortality and morbidity due to prostate cancer in asymptomatic men. The NHMRC review's conclusions included the following:[7]

> 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.*

The inconsistency in the findings of the two major 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[8] found a statistically non-significant 13% **increase** in prostate cancer 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)[9] found a statistically significant 21% **fall** in prostate cancer mortality after 11 years of follow-up in men 55–69 years of age offered PSA testing every two-to-four years, generally without DRE.

There is no way of resolving this inconsistency and reaching an evidence-based conclusion as to whether or not PSA testing is efficacious in reducing mortality from prostate cancer. For the purpose of this guideline, therefore, the Expert Advisory Panel resolved to proceed as though PSA testing were efficacious and reduces prostate cancer mortality to the extent estimated by ERSPC.[9] Several factors influenced this decision:

1. There are two aspects of study conduct that would cause PLCO to underestimate efficacy of PSA testing.[8] Of men randomised for PLCO, 45% had a PSA test in the three 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,[10] while an estimated 30.7% of the ERSPC control group was tested once or more during the Study.[11] 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,[12] while in ERSPC biopsy compliance was approximately 90%.[13]

2. The pattern of evolution of the difference in cumulative prostate cancer mortality between ERSPC intervention arm and control arm men is exactly that expected were PSA testing to be 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.[9]

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 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]

The ERSPC has recently published results from 13 years of follow-up.[14] While the estimated relative cumulative benefit at 13 years remains the same is it was at 11 years (a 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.[14] 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 at 13 years.[14] These are trends that would be expected from introduction of an effective cancer screening test because, while the extra cancers diagnosed begin on day 1, the benefits in terms of deaths prevented are not seen for a number years, some 6–7 years in the case of prostate cancer, and continue to accumulate for some years thereafter, depending on how long testing is continued.[15]

While reduction in mortality from cancer is the main benefit sought from an efficacious cancer screening test, there are other potential benefits that contribute to efficacy. 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 side-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.[7] More research is needed in this area.

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5.3.2 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 European Randomized Study of Screening for Prostate Cancer[14] and the Gøteborg prostate cancer screening trial.[16] 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.[17] 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 they have to be treated with the same seriousness as any cancer of their stage and grade.

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 the inconvenience, discomfort and occasional adverse effects on health (e.g. bleeding or infection) of a prostate biopsy when it is done to see if the positive test signifies cancer.

Treatment of a prostate cancer found following a positive test can be a cause of distress, discomfort and quite frequent adverse effects. 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.

The major adverse effects following prostate cancer treatment are:[18]

- urinary incontinence, particularly in men treated by radical prostatectomy or radiotherapy, which is common soon after treatment and persists in some 12–15% of men treated by radical prostatectomy

- 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 (about 15% after 3 years).

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5.3.3 Rates of PSA-based testing in Australia

Analysis of Medicare Benefits Schedule (MBS) records suggest that each year about 20% of men aged between 45 and 74 have a PSA test, presumably for the purpose of early diagnosis of prostate cancer. This estimate is based on the relevant Medicare Item number, recorded counts of which are fewer than the actual number of tests done.[19] By way of comparison, the latest figures from the Australian Institute of Health and Welfare show that the participation rate of eligible women (those 50–69 years of age) in the BreastScreen Australia program for 1997–1998 was 54.3%, which, being a program of biennial screening, averages at about 27% per year.[20] Hence, some have characterised Australia as having an unorganised de facto national program of screening for prostate cancer.

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 and/or limited life expectancy are still being tested.

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5.4 The need for a PSA testing guideline

In Australia now, there is no commonly accepted guidance for men about who should be tested for prostate cancer, at what ages and how frequently. Nor is there specific guidance for men in high risk groups, particularly men with a family history of the disease. 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 that decisions about what represents a positive test result are highly variable.

Best present evidence suggests that PSA testing can reduce deaths from prostate cancer by at least 21% in men 55–69 years of age and tested every 4 years in this age interval. PSA testing can detect the disease at a clinically localised stage and at a lower grade than is observed for prostate cancers detected in other ways. It has also been shown to reduce the rates of metastatic disease and subsequent use of androgen deprivation therapy, a treatment that can reduce symptoms from and the rate of progression of metastatic prostate cancer. Given this evidence, the current situation is far from ideal:

- Each year approximately 20% of men 45–74 years of age are tested for prostate cancer according to figures derived from Medicare Benefits Schedule data, presumably with the intent of early diagnosis intent.[21]

- 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.

- 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 3–7 men must be diagnosed with and treated for prostate cancer to prevent one death from prostate cancer. 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. This is a program of ongoing PSA 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.

- The needs of men 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 an acceptable balance between the benefits and harms of testing for early diagnosis of prostate cancer. We hope that implementation of these recommendations will help achieve this balance for Australian men.

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5.5 Purpose of this guideline

The purpose of this guideline is to produce evidence-based recommendations for PSA testing and immediately consequent clinical care in Australia. The aim of the recommendations, through their application in practice, is to maximise the benefits and minimise the harms from PSA testing of men without symptoms suggestive of prostate cancer.

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5.6 Intended users of this guideline

The target users of this guideline are health professionals in primary care, such as general practitioners, who are typically the first point of contact within the health care system for the majority of men, and medical and nursing practitioners working within the field of prostate cancer care in both diagnostic and treatment contexts. Target population

This guideline contains recommendations for PSA testing in asymptomatic men without known prostate cancer and early management of prostate cancer in men who have been diagnosed with the disease consequent to PSA testing.

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5.7 Healthcare setting to which this guideline applies

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

- primary care, including general practice and Aboriginal medical services

- urology services

- public and private hospitals.

The primary users of the guideline are general practitioners advising men who are considering testing or have chosen to be tested and urologists and other health practitioners who are advising men who have 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 is also intended for urologists, urology nurses, prostate cancer specific nurses, pathologists, radiation oncologists, people involved in communicating risk to people, policy makers, and hospital resource managers.

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5.8 Scope of this guideline

The guideline addresses the following areas:

- risk

- testing (PSA testing strategies, PSA test modality, criteria for withholding PSA testing, role of digital rectal examination, information and support for men considering a PSA test)

- investigations (indications for further investigations, prostate biopsy quality criteria, follow-up to negative prostate biopsy)

- management options (for men with biopsy-diagnosed prostate cancer choosing between an active surveillance protocol, a watchful waiting protocol or immediate potentially curative therapy)

- 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, List of clinical questions.

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5.9 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)*.[22]

Literature searches were conducted for each clinical question to identify evidence relevant to pre-specified populations, interventions (or exposure, for the risk question), 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 and men with different levels of socioeconomic status. 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. Expert Advisory Panel members and contributors and the statement of competing interests is available in Appendix 5. Conflict of interest summary. Details in regards to the funding, dissemination and recommended future updates of the guidelines are described in Appendix 1. Guideline development process.

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6 1 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 2)

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Cite this guideline

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.

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

6.1 Background

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.

However, 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.

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6.2 Evidence

Eleven retrospective cohort studies [6][7][8][9][10][11][12][13][14][15][16] and one nested case-control study [17] addressing the question and meeting the inclusion criteria were included in the systematic review: three used linked population-wide data from Sweden,[12][13][9] five used the Swedish Family-Cancer Database,[6][7][11][14][15] one each used linked data from Utah in the US,[17] Southern Sweden,[8]Iceland,[10] and Finland.[16] The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

All 11 retrospective cohort studies [6][7][8][9][10][11][12][13][14][15][16] (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 due to 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[17](level II evidence) was also low quality with high risk of bias. Three of the retrospective cohort studies[14][6][7] 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.

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6.2.1 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. 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. Two studies [10][17] that assessed family history in third-degree relatives reported risk ratios (RRs) 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 [10][17] reported RRs of 1.3–1.4 and 1.7 (with a lower 95% confidence limit below 1) when the affected relative was diagnosed at a younger age (< 68 years).

Generally, the RR was greater than 2.0 for affected first-degree relatives. The main variation in these estimates was higher values for diagnosis at a younger age, and lower values for diagnosis at an older age, for either the affected family member or the man at risk. Risk also increased as the number of affected family members increased. Therefore, 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. The RR was higher for younger men, those whose first-degree relative was diagnosed at a younger age and those with multiple affected first-degree relatives. While there was some inconsistency across studies, the increased risk was not clinically important (i.e. RR was less than 2) for those aged approximately 75–80 years or over. The risk was lower and not clinically important for men with only second- or third-degree relatives diagnosed with prostate cancer.

The observed association between family history and risk of a diagnosis of 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[9] 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[12] reviewed, the period of observation for the diagnosis of prostate cancer fell within the PSA testing era (after 1990). Because of this potential confounding of the association between family history and risk of a prostate cancer diagnosis, translating the observed estimates of increased risk into differences in risk for men with a family history may be erroneous (see Chapter 2). Studies that report 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.

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6.2.2 Prostate cancer-specific mortality

There was reasonable consistency in the overall association between family history in a first-degree relative and prostate cancer mortality, with RRs of mortality from prostate cancer ranging from approximately 2.0 to 2.75. Quite large associations were seen for multiple family members affected, especially at younger age. Overall, men with a first-degree relative (father or brother) diagnosed with prostate cancer had more than double the risk of dying from prostate cancer than men without this family history. Again the risk was greater when multiple first-degree relatives were affected or when the man at risk or his first-degree relative were diagnosed at younger ages.

Compared with findings for prostate cancer diagnosis, reported increases in prostate cancer mortality are less likely to be confounded by higher rates of PSA testing among asymptomatic men with family history. In contrast, there may be a small negative bias due to the protective effect of PSA testing against prostate cancer mortality. The implications of this increased risk in terms of offering a PSA test to asymptomatic men is discussed in detail in Chapter 2 (see 2.1 PSA testing strategies).

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6.2.3 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 impact on prostate cancer mortality.

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6.3 Evidence summary and recommendations

Evidence summary	Level	References
Risk of prostate cancer diagnosis	II, III-2	[6] , [7] , [8] , [9] , [10] , [11] , [12] , [13] , [14]

Evidence summary	Level	References
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 risk 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 increased risk was not clinically important (i.e. the relative risk less than 2) for those aged approximately 75–80 years or over. The risk was lower and not clinically important for men with only second- or third-degree relatives diagnosed with prostate cancer. Uncontrolled confounding by PSA testing is likely to bias estimates of relative risk of prostate cancer incidence upwards.		[15], [16], [17]
Risk of death from prostate cancer Men with a first-degree relative (father or brother) who was diagnosed with prostate cancer had more than double the risk of dying from prostate cancer than men without this family history. For an asymptomatic man with a family history of prostate cancer in a first-degree relative, the risk of death from prostate cancer was greater if multiple first-degree relatives were affected, if his first-degree relative was diagnosed at a younger age, or if he was diagnosed at a younger age.	III-2	[6], [7], [14]

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6.3.1 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.

Section 2.1.4 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 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.

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6.4 Discussion

Supporting attachments

6.4.1 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 risk of a diagnosis of prostate cancer is unknown.

6.4.2 Future research priorities

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

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[i] 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).

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6.1 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 2)**

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.

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Contents

6.1.1 Background

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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However, 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.

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6.1.2 Evidence

Eleven retrospective cohort studies [6][7][8][9][10][11][12][13][14][15][16] and one nested case-control study [17] addressing the question and meeting the inclusion criteria were included in the systematic review: three used linked population-wide data from Sweden,[12][13][9] five used the Swedish Family-Cancer Database,[6][7][11][14][15] one each used linked data from Utah in the US,[17] Southern Sweden,[8]Iceland,[10] and Finland.[16] The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

All 11 retrospective cohort studies [6][7][8][9][10][11][12][13][14][15][16] (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 due to 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[17](level II evidence) was also low quality with high risk of bias. Three of the retrospective cohort studies[14][6][7] 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.

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6.1.2.1 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. 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. Two studies [10][17] that assessed family history in third-degree relatives reported risk ratios (RRs) 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 [10][17] reported RRs of 1.3–1.4 and 1.7 (with a lower 95% confidence limit below 1) when the affected relative was diagnosed at a younger age (< 68 years).

Generally, the RR was greater than 2.0 for affected first-degree relatives. The main variation in these estimates was higher values for diagnosis at a younger age, and lower values for diagnosis at an older age, for either the affected family member or the man at risk. Risk also increased as the number of affected family members

increased. Therefore, 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. The RR was higher for younger men, those whose first-degree relative was diagnosed at a younger age and those with multiple affected first-degree relatives. While there was some inconsistency across studies, the increased risk was not clinically important (i.e. RR was less than 2) for those aged approximately 75–80 years or over. The risk was lower and not clinically important for men with only second- or third-degree relatives diagnosed with prostate cancer.

The observed association between family history and risk of a diagnosis of 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[9] 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[12] reviewed, the period of observation for the diagnosis of prostate cancer fell within the PSA testing era (after 1990). Because of this potential confounding of the association between family history and risk of a prostate cancer diagnosis, translating the observed estimates of increased risk into differences in risk for men with a family history may be erroneous (see Chapter 2). Studies that report 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.

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6.1.2.2 Prostate cancer-specific mortality

There was reasonable consistency in the overall association between family history in a first-degree relative and prostate cancer mortality, with RRs of mortality from prostate cancer ranging from approximately 2.0 to 2.75. Quite large associations were seen for multiple family members affected, especially at younger age. Overall, men with a first-degree relative (father or brother) diagnosed with prostate cancer had more than double the risk of dying from prostate cancer than men without this family history. Again the risk was greater when multiple first-degree relatives were affected or when the man at risk or his first-degree relative were diagnosed at younger ages.

Compared with findings for prostate cancer diagnosis, reported increases in prostate cancer mortality are less likely to be confounded by higher rates of PSA testing among asymptomatic men with family history. In contrast, there may be a small negative bias due to the protective effect of PSA testing against prostate cancer mortality. The implications of this increased risk in terms of offering a PSA test to asymptomatic men is discussed in detail in Chapter 2 (see 2.1 PSA testing strategies).

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6.1.2.3 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 impact on prostate cancer mortality.

6.1.3 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 risk 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 increased risk was not clinically important (i.e. the relative risk less than 2) for those aged approximately 75–80 years or over. The risk was lower and not clinically important for men with only second- or third-degree relatives diagnosed with prostate cancer. Uncontrolled confounding by PSA testing is likely to bias estimates of relative risk of prostate cancer incidence upwards.	II, III-2	[6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17]
Risk of death from prostate cancer Men with a first-degree relative (father or brother) who was diagnosed with prostate cancer had more than double the risk of dying from prostate cancer than men without this family history. For an asymptomatic man with a family history of prostate cancer in a first-degree relative, the risk of death from prostate cancer was greater if multiple first-degree relatives were affected, if his first-degree relative was diagnosed at a younger age, or if he was diagnosed at a younger age.	III-2	[6], [7], [14]

6.1.3.1 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.

Section 2.1.4 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 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.

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6.1.4 Discussion

Supporting attachments

6.1.4.1 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 risk of a diagnosis of prostate cancer is unknown.

6.1.4.2 Future research priorities

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

6.1.5 References

1. ↑ Cuzick J, Thorat MA, Andriole G, Brawley OW, Brown PH, Culig Z, et al. *Prevention and early detection of prostate cancer.* Lancet Oncol 2014 Oct;15(11):e484-92 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25281467.
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[i] 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).

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6.2 Discussion

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6.2.1 Chapter 1 Risk

6.2.2 Discussion

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Developing an effective and acceptable approach for testing to detect early prostate cancer in men attending primary care involves determining:

- which strategies for prostate-specific antigen (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, 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 indication for biopsy
- which further PSA tests (e.g. free-to-total PSA, 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
- which methods of decision support for men increase their capacity to make an informed decision whether to undergo PSA testing.

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7.1 Introduction

Developing an effective and acceptable approach for testing to detect early prostate cancer in men attending primary care involves determining:

- which strategies for prostate-specific antigen (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

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- the role of digital rectal examination (DRE), if any, in association with PSA testing
- which further PSA tests (e.g. free-to-total PSA, 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 indication for biopsy
- which further PSA tests (e.g. free-to-total PSA, 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
- which methods of decision support for men increase their capacity to make an informed decision whether to undergo PSA testing.

7.2 2.1 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 question 1)**

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7.2.1 Background

Decision support interventions and/or decision aids aim to help people make an informed decision about a screening or treatment intervention by providing information about the benefits, 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 via nurse or physician).[1]

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7.2.2 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][10][12][6][8][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 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] Three of the five randomised controlled trials that measured men's satisfaction about their decision-making reported significant increases.[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.

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7.2.3 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 limitations 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 limitations 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, had no demonstrable benefit on the decisional uncertainty men experienced when considering the benefits and limitations of PSA testing.	II	[4], [10], [14], [9]
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], [10], [6], [9], [7]

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 potential benefits and risks of PSA testing before the decision to test is confirmed.	C

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7.2.3.1 Health system implications of these recommendations

7.2.3.1.1 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 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 incorporating a training program on PSA testing and counselling into nursing/health science courses, or upskilling of existing professionals with the appropriate skills and knowledge.

7.2.3.1.2 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.

7.2.3.1.3 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).

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7.2.4 References

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7.2.5 Discussion

Supporting attachments

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7.3 2.2 PSA Testing strategies

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 4.1)**

- *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 question 4.2)**

- *does a PSA level measured at a particular age in men assist with determining the recommended interval to the next PSA test?* **(PICO question 4.3)**

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Contents

7.3.1 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 for early cancer may also bring to light cancers that would otherwise never have become clinically evident in the patient's lifetime.

The operation of the above factors means that 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. A systematic review of the available randomised controlled trials was the primary source of evidence used to answer PICO question 4.1.

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 4.1.

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 and specificity, 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 4.2, 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 4.3.

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7.3.2 Evidence

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

7.3.2.1.1 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 PSA testing reduces mortality from 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*.

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The largest of the trials was ERSPC,[8] a multicentre trial with seven centres. It found that, 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 ratio (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 (0.87–1.36).

Taken together, the results of the PLCO,[3] Norrköping,[9] Stockholm[2] and Quebec[6] trials are not consistent statistically with those of the ERSPC.[8] In addition, the PLCO,[3] although rated at moderate risk of bias, is weakened by a high rate of prior PSA testing of participants (45%), continuing PSA testing of men in the control arm (52% at the time of the last intervention round of testing), and a high level of non-compliance with biopsy recommendations (59.9% one year after a positive PSA test).[11]

These weaknesses appear to have been less in the ERSPC.[8] Based on the ERSPC Rotterdam centre,[7] 30.7% of ERSPC control participants had a PSA test once or more during the study period and biopsy compliance was approximately 90%. In addition, there was a high level of consistency among results from individual ERSPC centres, which followed similar, but not uniform protocols, and had their own investigator groups. For six of seven centres, RRs of prostate cancer-specific mortality for testing compared with no testing ranged from 0.56 to 0.89.[8] The seventh was an outlier (RR 2.15; 95% CI 0.19–23.8), based on 2 prostate cancer deaths in men offered PSA testing and 1 in men not offered it).[8] The 95% confidence intervals for prostate cancer-specific mortality among the ERSPC centres substantially overlapped.[8] Moreover, cumulative prostate cancer mortality in the control arm of the ERSPC has consistently diverged from that in the intervention arm after 7 years from trial entry.[5][7][8]

On the basis of our analysis, the ERSPC results, which suggested that PSA testing had a protective effect against prostate cancer mortality,[8] were considered to be the most reliable.

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7.3.2.1.2 Metastases at diagnosis reported in randomised controlled trials

Three trials (ERSPC, PLCO and the Norrköping trial)[8][9][11] 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 screening 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), with DRE for the first four years.

- ERSPC,[12] (RR 0.50; 95% CI 0.41–0.62) with screening 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.

Screening 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, the screening 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,[12] 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.

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7.3.2.1.3 Interpreting the randomised controlled trial findings

Given that greater reliance was placed on the finding of the ERSPC, and that this trial showed a benefit for screening, 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 enrolled men 55–69 years of age.
- The recommended screening interval was 4 years for all centres except Sweden, 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 screening round.
- Each ceased testing at 70–75 years of age.

Therefore, ERSPC results can be taken as indicative of the outcome of a policy of 4-yearly testing of men 55–69 years of age, referring men for biopsy when total PSA was > 3.0 ng/mL and ceasing screening at 70–75 years of age. The published results of different ERSPC centres generally give little indication of consistent variation in effect due to variation in the testing protocol. However, it may be inferred that the protocol used by the ERSPC Gøteborg centre was superior: broadly, this involved testing from 50 years of age at 2-year intervals, using PSA ≥ 2.9 ng/mL (WHO calibration, 1999–2004) as the criterion for biopsy, and cessation of screening at 70 years of age. The RR from the Gøteborg centre was 0.56 (95% CI 0.38–0.83),[8] the upper 95% confidence bound being just a little above the ERSPC RR point estimate of 0.79,[8] and its difference in cumulative hazard of death from prostate cancer (Nelson-Aalen method) to 14 years between intervention and control groups was –0.0039[5] – appreciably greater than that for the ERSPC as a whole (–0.0024).[8] In addition, the RR of prostate cancer death in the Gøteborg centre was the same, whether based on the full study population screened at age 50–69 years (RR 0.56; 95% CI 0.39–0.82), or its ERSPC core group members screened at age 55–69 years (RR 0.56; 95% CI 0.38–0.83).[5][8]

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7.3.2.1.4 Modelling studies

In addition to the evidence from randomised and pseudo-randomised controlled trials, three modelling studies [13][14][15][16] met the inclusion criteria for this review: 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 of the 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[16][14] and two were based on the Fred Hutchinson Cancer Research Center (FHCRC) microsimulation model of prostate cancer.[13][15] None of these studies were developed and calibrated for Australian context, or validated in Australia. The MISCAN model was based on the Dutch population and calibrated mainly to Dutch and other European data; levels of participation in testing were assumed to be 100%[16] and 80%[14]. The FHCRC studies were based primarily in the US population and were calibrated to US data, although one study[13] used initial treatment data for British Columbia. 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,[16] men up to 100 years of age with age distribution according to the European Standard Population,[14] contemporary men in the USA aged 40 years[15] and men in British Columbia aged 40 years.[13] 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 were found to adequately simulate prostate cancer incidence and mortality with the caveats that neither model incorporated realistic screening behaviours and 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.

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7.3.2.1.5 Modelling to predict effect of testing protocols on outcome death from prostate cancer

Tables 2.1–2.3 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 (FP) 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 directly by probability of one or more FPs. Mean months of life gained per man diagnosed measures the balance of benefit, in terms of life gained, to harm, in terms of over-diagnosis. In addition, it 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 or its Gøteborg centre has been highlighted in each table to provide a directly evidence-based 'anchor' with which to compare the possible alternative protocols.

Table 2.1 summarises the three alternative protocols based on the MISCAN model.[14] 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 FP 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 2.2, which summarises protocols from the Pataky et al model,[13] suggests that all protocols with higher probability of prevention of death from prostate cancer (up to 27% higher) achieve that at a cost in terms of increase in the percentage of men with more than one FP and reduction in means months of life gained by 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 in these men, is accompanied by a fall in percentage of men with more than one FP and quite a small fall in mean months of life gained per man diagnosed across all men covered by this protocol.

Table 2.3 summarises the much larger number of protocols examined by Gulati et al.[15] The most notable feature of these protocols is that using > 95th percentile of PSA as the criterion for further investigation consistently results in the lowest percentage of men with one or more FP and the highest mean months of life gained per man diagnosed in each age and frequency of testing band. These protocols' values for probability of death from prostate cancer prevented, however, are usually at the low end of the range. There is, therefore, a clear trade-off of benefit and harm here, although the generally high levels of mean months of life gained per man diagnosed suggest that it is net beneficial. Therefore, changing the criterion for further investigation from ≥ 3.0 ng/mL to > 95th percentile for age could be justified. For protocols testing men 40–69 years of age the probabilities of prostate cancer prevented, percentage of men with one or more FP, and mean months of life gained per man diagnosed were generally similar to those for protocols testing men 50–69 years of age.

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

Heijnsdijk 2009[16] modelled the effects of different test protocols on initial treatments including palliative therapy for those with metastatic disease at diagnosis. 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 receiving palliative therapy for metastatic disease at diagnosis at a cost of 149 additional unnecessary biopsies per 1000 men tested. Extending the testing age range to 75 years or increasing the frequency of testing to annually resulted in modest increases in the reduction of metastatic disease in diagnosis to 3.0 men and 2.6 men respectively per 1000 men tested accompanied by increases in the number of additional unnecessary biopsies of 230 and 185 respectively per 1000 men tested. This study did not model PSA levels of 4.0 ng/mL or age-specific percentiles as thresholds for biopsy or report numbers over-diagnosed or years or months of life gained.

Expressed in approximately equivalent terms to those of Table 2.2, increasing testing from four-yearly to yearly increases the probability that diagnosis with metastatic prostate cancer is prevented by 0.09 percentage points and extending the age range for testing to 75 years increases this probability by 0.05 percentage points at the 'cost' of an increase in probability of having an unnecessary biopsy of 3.6 and 8.1 percentage points, respectively.

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Table 2.1. 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

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	Mean months of life gained per man diagnosed
1	55–74	~3ng/mL	1 year	57.3	7.2	1.10	0.98§	7	12.8
2	55–69	~3ng/mL	1 year	44.8	4.5	0.90	0.88§	5	19.5
ERSPC‡	55–69	~3ng/mL	4 years	36.7	2.9	0.60	0.62§	5	20.8

Source: Heijnsdijk et al (2012)[14]

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

[FOOTNOTES TO BE PART OF PDF]

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 Pataky et al 2014

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	Mean months of life gained per man diagnosed
10	40–74	PSA ≥ 3.0 ng/mL	2 years	22.8	3.4	0.70	0.81§	4.86	23.8
15	50–74	PSA ≥ 3.0 ng/mL	2 years	22.5	3.2	0.68	0.80§	4.71	25.0
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 24.9 20 55–74 PSA ≥ 3.0 ng/mL 2 years 21.7 2.9 0.64 0.74§ 4.57 25.3 23 60–74 PSA ≥ 3.0 ng/mL 2 years 22.1 3.2 0.63 0.69§ 4.97 22.0 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 32.0 31 50–74 PSA ≥ 3.0 ng/mL 4 years 21.8 2.5 0.55 0.64§ 4.57 25.5 32 Gøteborg‡ 50–69 PSA ≥ 3.0 ng/mL 2 years 19.1 2.1 0.55 0.71§ 3.79 34.1 43 50–74 PSA ≥ 3.0 ng/mL up to age 69 years and PSA ≥ 4.0 ng/mL for men aged ≥ 70 years 4 years 15 1.4 0.44 0.57 § 3.28 39.5 47 55–69 PSA ≥ 3.0 ng/mL 4 years 15.5 1.1 0.37 0.49§ 2.99 44.3

Source: Pataky et al (2014)[13]

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

[asterisk]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 % = percent of men having an over-diagnosed prostate cancer during the age range of testing

Probability that prostate cancer death is prevented % = percent of men prevented from dying from prostate cancer from date of first testing to age 90[13]

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 screening strategy used in the Gøteborg centre of the ERSPC

§ Pataky et al (2014)[13] 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 2.3. Modelled outcomes of a range of PSA testing protocols sorted in decreasing order of probability of death from prostate cancer prevented reported by Gulati et al 2013

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

In the ERSPC,[8] screening protocols using PSA thresholds of 2.5–4.0 ng/mL as the criterion for biopsy reduced prostate cancer mortality, compared with no screening. To determine whether a specific optimal PSA threshold could be identified, studies comparing the performance characteristics of PSA thresholds less than or equal to 4.0 ng/mL were examined. They were restricted to reports from the ERSPC centres that demonstrated reduced prostate cancer mortality with PSA testing (Rotterdam and Gøteborg),[8] and studies that biopsied men regardless of PSA levels of which there was one. As these studies employed only a sextant biopsy, studies in which biopsies were performed for all men with PSA results in a specified range and employed a biopsy with more than 6 cores were also included.

Eight level III-2 diagnostic performance studies met the inclusion criteria.[17][18][19][20][21][22][23][24] All were at moderate risk of bias.

In one study,[22] the placebo arm of the Prostate Cancer Prevention Trial, 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 screened annually for 7 years and offered a sextant biopsy at the end of the trial.[22] Potential verification bias was considered and shown not to be an issue.[22]

The remaining seven studies were able to provide estimates only of increases in numbers of cancers detected and numbers of unnecessary biopsies with decreasing PSA thresholds.[20][17][18][19][21][24][23] 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.[18][17][19][21][24][23] In the remaining study, all men with a family history of prostate cancer and a PSA below a specified PSA threshold underwent prostate biopsy.[20]

Only the ERSPC described how the PSA assay used was calibrated;[19] World Health Organization (WHO) calibration, applied retrospectively. WHO calibration could be inferred for another two studies from information available on the assay (Izotope) manufacturer's website.[18][23] Two studies did not report the PSA assay used. [17][24] Only one study compared yields stratified by Gleason Score at different PSA thresholds.[22]

Comparisons between studies in terms of absolute numbers were limited due to differing biopsy protocols, populations and PSA assays and their calibration and thus this review focuses on the effects of varying thresholds within studies. In all eight studies, lowering the PSA threshold increased cancer detection at a cost of increased unnecessary biopsies.[17][18][19][20][21][24][23][22] In six of the eight studies the ratio of false positives to true positives (FP:TP ratio) increased as the PSA threshold changed from 4.0 ng/mL to 3.0 or 2.5 ng/mL. In two studies in which lower PSA levels were assessed, the FP:TP ratio increased more rapidly as the threshold was reduced from 3.0 ng/mL to 2.0 ng/ml, and more rapidly again as it was reduced from 2.0 ng/mL to 1 ng/mL. The FP:TP ratio 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.[19][18][24][22]

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Figure 2.1. Plots of the FP:TP ratios at each PSA threshold in the 8 studies reviewed.

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Data from references[19][18][17][20][22][23][24][21]

Greatest weight was given to the Prostate Cancer Prevention Trial,[22] which provided the most complete data for a repeatedly screened cohort and the most conservative estimates, and the ERSPC[19] which reported data for previously screened cohorts and obtained using PSA measurements adjusted to the WHO standard. In the Rotterdam ERSPC cohort of men aged 54–74 years who had been screened 4 years previously, lowering the threshold from 4.0 ng/mL to 3.0 ng/mL (WHO calibration) resulted in 3.77 additional unnecessary biopsies for every additional cancer detected with 14 additional cancers detected and 52 additional unnecessary biopsies per 1000 men screened.[19]

At the other end of the spectrum, in the Prostate Cancer Prevention Trial[22] placebo arm of repeatedly screened 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: 2.17 additional unnecessary biopsies for every additional cancer detected, 26 additional cancers detected and 56 additional unnecessary biopsies per 1000 men screened. For men aged over 69 years the gains in sensitivity were greater (13.2 percentage points) for a similar decrease in specificity (7.7 percentage points).[22]

When the threshold was lowered from 3.0 ng/mL to 2.0 ng/mL in the Prostate Cancer Prevention Trial[22] 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.[22] Similar effects were seen in a cohort of men with PSA less than 4.0 ng/mL and a family history of prostate cancer.[20] 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[22] resulted in 2.26 and 2.39 additional unnecessary biopsies for every additional cancer detected respectively.[22]

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:[22] lowering the PSA threshold to 3.0 ng/mL increased the sensitivity for 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 any cancer by 20.0 percentage points, whereas the sensitivity for cancer with a Gleason score > 6 increased by 26.8 percentage points and cancer with a Gleason score > 7 by 28.0 percentage points. Improvements in detection of cancer with Gleason score > 6 were even higher for men over 69 years of age: 23.0 % (if threshold is dropped from 4.0 to 3.0 ng/mL) and 30.2% (if threshold is dropped from 4.0 to 2.5 ng/mL). In contrast further reduction from 3.0 to 2.0 ng/mL did not result in greater increases in sensitivity for higher grade disease.[22]

Considerable weight has been given to the Prostate Cancer Prevention Trial study.[22] However, there are two caveats to the application of these results to population-based prostate cancer testing in Australia. Firstly, participants had PSA levels of 3.0 ng/mL or less, a normal DRE and a American Urological Association symptom score less than 20 prior to screening and thus may not represent a population based screening population.

Secondly, Hybritech PSA assays were used and it was not reported how these assays were calibrated. As PSA measurements vary with assay type and calibration, the absolute values for PSA measurements reported in the Prostate Cancer Prevention Trial study[22] 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. A similar caveat may also apply to results of the ERSPC Rotterdam centre[19] as it used a Hybritech assay, although the results were retrospectively adjusted to the WHO standard.

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7.3.2.3 Determining optimal PSA testing intervals based on age

Two level III-2 studies[25][26] reported the risk of prostate cancer mortality for PSA levels at ages less than 56 years. One was a retrospective cohort study of participants in the Copenhagen City Heart Study.[25] 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.[26] This study was at high risk of bias. It used a retrospective cohort design to assess of 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 focussed on men from approximately 40–55 years of age at testing and a maximum of 20 years follow-up, since its primary purpose was to obtain data relevant to PSA testing over about a 20-year period from first testing. In the Copenhagen City Heart Study[25] 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[26]} 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, [26] the authors assumed that screening 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.[25][26]

The studies[25][26] 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 radical 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 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 of use of PSA for the early detection of prostate cancer. Given the present extent of PSA testing for early detection of prostate cancer in Australia, this body of evidence has the potential to inform specification of PSA testing protocols that achieve a better balance of benefits to harms than there is likely to be in present testing practice.

Table 2.4 summarises estimates of increments in absolute percentage cumulative risk of prostate cancer death above the risk at a baseline PSA of < 1 ng/mL[25] or the lowest quarter of the PSA distribution[26] by age, length of follow-up and baseline PSA level. While the Copenhagen City Heart Study[25] reported on cumulative risk for three PSA levels; from > 3 to 4 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[26] lay consistently in the range 1.0–3.0 ng/mL. The results in the table suggest the following:

- Risk increments for comparable baseline PSA levels in the Copenhagen City Heart Study[25] at 10 years and the Malmö Preventive Project[26] at 15 years are similar but tending to be higher in the Malmö Preventive Project,[26] 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 37.5–42.5 years of age in the Malmö Preventive Project[26] are small (0.1% to 0.8%) for both 15 and 20 years of follow-up.

- These increments are 1–2 times greater at 15 years and 3–4 times greater at 20 years in men 45–49 years of age and 6–12 times greater at both 15 and 20 years in men 51–55 years of age.

Table 2.4. 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

Study Age (years) Length of follow-up (years) Reference PSA level Compared PSA level 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) Orsted et al, 2012 < 45 10 ≤ 1.0 ng/mL 0.3 > 1.0–2.0 ng/mL 0.3 > 2.0–3.0 ng/mL 1.2 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 Highest tenth, ≥ 1.30 ng/mL 0.5 20 Highest quarter, ≥ 0.90 ng/mL 0.24 Highest tenth, ≥ 1.30 ng/mL 0.8 Orsted et al, 2012 45–49 10 ≤ 1.0 ng/mL 0.4 > 1.0–2.0 ng/mL 0.6 > 2.0–3.0 ng/mL 2.0 Vickers et al, 2013 45–49 15 Lowest quarter, ≤ 0.44 ng/mL 0.08 Highest quarter, ≥1.1 ng/mL 0.23 Highest tenth, ≥ 1.6 ng/mL 0.66 20 0.24 Highest quarter, ≥ 1.1ng/mL 0.94 Highest tenth, ≥ 1.6ng/mL 2.18 Orsted et al, 2012 50–54 10 ≤ 1.0 ng/mL 0.5 > 1.0–2.0 ng/mL 0.8 > 2.0–3.0 ng/mL 2.7 Vickers et al, 2013 51–55 15 Lowest quarter, ≤ 0.53 ng/mL 0.33 Highest quarter, ≥ 1.4 ng/mL 1.47 Highest tenth, ≥ 2.4 ng/mL 3.05 20 0.57 Highest quarter, ≥ 1.4 ng/mL 2.41 Highest tenth, ≥ 2.4 ng/mL 5.11

Sources: Orsted et al (2012)[25], Vickers et al (2013)[26]

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7.3.2.4 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 screening at an earlier age than men at average risk, typically 45 years of age when average risk men are advised to begin screening at 50 years of age. 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) 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 50 years of age, and from which risk would be expected to evolve with age in the same way as it would evolve from 50 years of age in men at average risk. In principle, by beginning PSA testing at this age, the high-risk men could expect the same benefit, and probably harm, from testing as average risk men starting testing at 50 years of age.

Using present incidence or mortality rates for prostate cancer, it is arguably not possible to identify accurately the age at which men at, say, 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 due to 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 men at average risk, the annual average prostate cancer mortality rates for Australia in 1991 to 1995, the five-year period of peak prostate cancer mortality, were chosen. 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 2.5 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).[27] For ages 40 and 45 only, Table 2.5 also includes estimates for men with varying levels of higher than average risk of prostate cancer - relative risks from 2.0 to 5.0. A period of 10 years of life was chosen because most recent 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 2.5 indicates that a 45 year-old man at three-times the average risk of prostate cancer would have increase in his annual risk of prostate cancer death of 23.94 per 100,000 over the next 10 years of his life from the very low rate at 45 years of age. This increase is a little higher than the corresponding increase for an average-risk man starting PSA testing at 50 years of age (22.69 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 19.95 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. In 40-year-old men, even at a five-times increase in risk of prostate cancer, the increase in annual risk of death from prostate cancer over the next 10 years is much less than it is in average-risk 50-year-old men.

Table 2.5. Estimated increase in prostate cancer mortality rate (annual number of deaths per 100,000 men) over the 10 years of age after each of ages 40, 45 and 50 years in Australian men at average risk of prostate cancer, and after each of 40 and 45 years of age in men at two- to five-fold increased risks of prostate cancer

Relative risk of prostate cancer	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)	2.34	7.98	22.69[†]
2.0	4.67	15.96	
2.5	5.84	19.95	
3.0	7.01	23.94	
3.5	8.18	27.93	
4.0	9.34	31.92	
5.0	11.68	39.91	

[†]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 40 and 45 years of age at various degrees of increased risk of prostate cancer.

Data from Australian Institute of Health and Welfare (2014) [27]

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7.3.3 Evidence summary and recommendations

Evidence summary	Level	References
For men 50–69 years of age without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, PSA testing every 2–4 years and a PSA threshold for biopsy of > 3.0 ng/mL reduced prostate cancer mortality.	II, III-2	[1], [2], [9], [10], [8], [12], [7], [6], [5], [4], [28], [3]
The modelling studies were not considered to provide evidence independent of the empirical data on which they were based. [§]Unspecified evidence level	N/A	[14], [13], [16], [15]

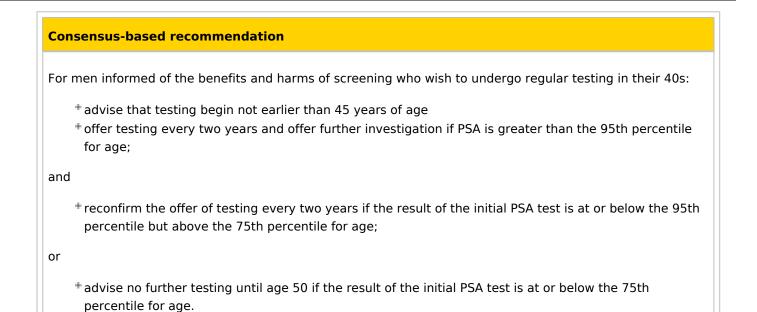| Evidence summary	Level	References
As the PSA threshold for referral to biopsy was reduced from 4.0 ng/mL the ratio of false positive to true positive tests increased. The rate of increase in this ratio appeared to become greater as the threshold PSA level was progressively reduced. Thus, any reduction 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	[20], [17], [18], [19], [22], [23], [24], [21]
In men 37.5–42.5 years of age, 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 45–49 years of age, 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 51–55 years of age: 1.5% and 3.1% at 15 years and 2.4% and 5.1% at 20 years.	III-2	[25], [26]

[§]NHMRC classification of levels of evidence does not currently encompass modelling studies

Evidence-based recommendation	Grade
For men informed of the benefits and harms of screening who wish to undergo regular testing, offer PSA testing every two years from age 50 to age 69, and offer further investigation if the 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

For men informed of the benefits and harms of screening who wish to undergo regular testing in their 40s:

- advise that testing begin not earlier than 45 years of age
- offer testing every two years and offer further investigation if PSA is greater than the 95th percentile for age;

and

- reconfirm the offer of testing every two years if the result of the initial PSA test is at or below the 95th percentile but above the 75th percentile for age;

or

- advise no further testing until age 50 if the result of the initial PSA test is at or below the 75th percentile for 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:

- offer testing every two years from 45–69 years of age rather than 50–69 years of age;
- offer further investigation if PSA is greater than the 95th percentile for age

and

- reconfirm the offer of testing every two years if the result of the initial PSA test is at or below the 95th percentile for age but above the 75th percentile for age;

or

- advise no further testing until age 50 if the result of the initial PSA test is at or below the 75th percentile for age.

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7.3.3.1 Health system implications of these recommendations

7.3.3.1.1 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,[29] 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 risks and potential benefits could lead to less frequent testing and fewer false positive tests.

7.3.3.1.2 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.

7.3.3.1.3 Barriers to implementation

No barriers to implementation of these recommendations are foreseen.

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7.3.5 Discussion

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7.4 2.3 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 question 6)**

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7.4.1 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 the question: Does DRE still have an important role in the detection of asymptomatic prostate cancer?

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7.4.2 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 screening 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 which 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 screened, 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 screened. Importantly, the same increase in cancer detection rate could have been achieved without DRE, but instead by 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

Rates of true and false positive results for PSA only (blue line) and PSA + DRE (orange line)

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 degree of screening, and verification prevent pooling of the data and limit direct comparison.

Four studies[1][4][2][5] reported the effects of adding DRE to a screening 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 screened, adding DRE to a screening protocol with PSA threshold of 4.0 ng/mL would detect 3 additional cancers with Gleason Score > 7 and 7 additional cancer with Gleason Score > 6. The proportion of higher-grade cancers amongst the additional cancers detected with DRE was lower than, or similar to, that detected using PSA alone: 23.2% cancers with Gleason Score > 6 and 9.0% cancers with Gleason Score > 7, compared with rates detected by 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 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, an 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.

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7.4.3 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 test 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 still has an important role in assessing the prostate prior to biopsy in a specialist setting.

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7.4.3.1 Health system implications of these recommendations

7.4.3.1.1 Clinical practice

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

7.4.3.1.2 Resourcing

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

7.4.3.1.3 Barriers to implementation

No barriers to the implementation of this recommendation are foreseen.

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7.4.4 References

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7.4.5 Discussion

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7.5 2.4 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 question 17.1)**

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7.5.1 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).

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7.5.2 Evidence

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 reduced mortality up to 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 50–69 aged 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]

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7.5.3 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 at 6–7 years after the start of PSA testing.	II	[4], [1], [2], [3]

Evidence-based recommendation	Grade
Do not offer PSA testing to a man who is unlikely to live another 7 years.	C

Practice point
When discussing the potential benefits and harms with a man over 69 years of age or with a potentially fatal chronic illness who is considering PSA testing, explain that: only prostate cancer death more than seven years in the future could be prevented by testing; there might be earlier benefits to quality of life through avoidance of diagnosis of an advanced prostate cancer; and either benefit would come with the possibility of poorer quality of life due to harmful consequences of treatment for prostate cancer.

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7.5.3.1 Health system implications of these recommendations

7.5.3.1.1 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.[5] 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.

7.5.3.1.2 Resourcing

Implementation of this recommendation would have no significant resource implications.

7.5.3.1.3 Barriers to implementation

No barriers to the implementation of this recommendation are foreseen.

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7.5.4 References

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7.5.5 Discussion

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7.6 2.5 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 less than the threshold 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 elevated total PSA result? **(PICO question 14.1 b)**

For asymptomatic men with an initial total PSA less than the threshold 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? **(PICO question 14.2 b)**

For asymptomatic men with an initial total PSA less than the threshold 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? **(PICO question 14.3 b)**

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7.6.1 Background

For men without a diagnosis or symptoms of prostate cancer who, after being informed of the benefits and harms of screening, wish to undergo regular PSA testing, the following strategy is recommended because is associated with reduced risk of death from prostate cancer: offer PSA testing every two to four years from age 50 to age 69, and offer further investigation if the PSA is greater than 3 ng/mL (see 2.1 PSA Testing strategies).

In asymptomatic men without a diagnosis of prostate cancer, a single total PSA (tPSA) 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 PSA levels below 3.0 ng/mL.[2]

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7.6.1.1 Free-to-total PSA %

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% free) are likely to have prostate cancer. Measurement of the ratio of free to total PSA expressed as a percentage (f/tPSA%), has been used as a method of improving the predictive efficiency of PSA testing. For example, f/tPSA% might be used in men with tPSA below 3.0 ng/mL to improve sensitivity. The Finnish centre of the ERSCP trial found that f/tPSA% was a strong predictor of the later diagnosis of prostate cancer in men with a PSA level below 3.0 ng/mL.[3]

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7.6.1.2 PSA velocity and other measures of PSA kinetics

The rate of increase in serum tPSA has been identified as a risk indicator for prostate cancer.[4] PSA velocity has been defined as the absolute increase in tPSA 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 tPSA doubling time (e.g. using a doubling time less than three years as an indicator of increased risk) or 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 tPSA 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, as when PSA velocity is measured. 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]

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7.6.1.3 Prostate Health Index (PHI)

PHI testing differs from tPSA testing and f/tPSA% testing in identifying whether the free PSA proportion in serum contains an abnormally high component of preforms of PSA, specifically pro2PSA. The PHI is calculated as follows:

(pro2PSA/free PSA) * log (tPSA)

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 tPSA levels are low, such as when tPSA is below the 3.0 ng/mL threshold. Therefore, the use of PHI might be expected to improve the sensitivity of PSA testing.

7.6.2 Evidence

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

7.6.2.1 Free-to-total PSA %

Four diagnostic accuracy studies were identified that reported the numbers of additional cancers detected and biopsies undertaken as a result of f/tPSA% 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.

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

In a Japanese study[6] of men aged 50–79 years, the use of a f/tPSA% threshold of < 12% for men with a tPSA 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 not considered to be generalisable to the Australian screening populations because the cancer detection rate for men with a tPSA greater than 4.0ng/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 f/tPSA% threshold of < 16% for men with a tPSA 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 tPSA 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 tPSA threshold of 3.0ng/mL, as it did not did not seek to improve on the sensitivity at tPSA 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 tPSA levels less than a threshold of 4 ng/mL, the use of a f/tPSA% 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.

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7.6.2.2 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 the threshold for biopsy.

7.6.2.3 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 the threshold for biopsy.

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7.6.3 Evidence summary and recommendations

Evidence summary	Level	References
Free-to-total PSA	III-2	[6], [7], [8], [9]

Evidence summary	Level	References
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 f/tPSA < 27% as the criterion for biopsy in those with tPSA between 2.0 and 4.0 ng/mL, more than doubled the number of cancers detected, compared to the use of a PSA threshold of 4.0 ng/mL alone, and resulted in approximately one extra unnecessary biopsy for each additional cancer detected. A study in men at average risk of prostate cancer found that the additional biopsy criterion of low f/tPSA% (<12%) for men with a tPSA 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 tPSA > 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 tPSA threshold of 4.0 ng/mL.		
PSA velocity There was no evidence for whether or not measuring the PSA velocity of men with a normal PSA improves the detection of prostate cancer, with PSA alone.	N/A	
Prostate health index There was no evidence for whether or not PHI testing men with a normal PSA improves the detection of prostate cancer, compared with PSA alone.	N/A	

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 the free-to-total PSA ratio is < 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.

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7.6.3.1 Health system implications

7.6.3.1.1 Clinical practice

The use of f/tPSA% as an adjunct to tPSA testing in high risk men with tPSA levels between 2.0–3.0 ng/L is not currently a routine approach.

7.6.3.1.2 Resourcing

Implementation of the recommendations about f/tPSA% tests men at high risk of prostate cancer and tPSA levels between 2.0–3.0 ng/mL will not have any resource implications.

The f/tPSA% test is reimbursable in Australia.

7.6.3.1.3 Barriers to implementation

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

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7.6.4 References

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7.6.5 Discussion

Supporting attachments

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7.7 2.6 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 the threshold, 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 elevated total PSA result? **(PICO question 14.1 a)**

For asymptomatic men with an initial total PSA above the threshold, does measuring PSA velocity improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single elevated total PSA result? **(PICO question 14.2 a)**

For asymptomatic men with an initial total PSA above the threshold, 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? **(PICO question 14.3 a)**

***For asymptomatic men with an elevated total PSA test, does repeating the total PSA test and using an elevated initial and repeat total PSA as the indication for biopsy improve relative specificity without compromising prostate cancer or high-grade prostate cancer detection, when compared with a single elevated total PSA result as the indication for biopsy*? (PICO question 14.4)**

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7.7.1 Background

A tPSA threshold of 4.0 ng/mL has traditionally been used as the criterion for prostate biopsy. The current trend towards the use of lower tPSA 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 tPSA 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 tPSA level above 3.0 ng/mL. Because of the analytical and biological variability of tPSA, including the chronological rise in PSA in men in their sixties, this review focused on studies that used tPSA thresholds between 2.0 and 4.0 ng/mL or age-specific thresholds. Restricting the evidence to studies that used a tPSA threshold of 3.0 ng/mL would have limited the evidence and would not have taken into account the analytical variability of the tPSA 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/efficacy of the recommended PSA testing strategy. As a result, studies using a single tPSA threshold were restricted to those whose participants had a tPSA < 5.5 ng/mL unless there were analyses for older men (who are more likely not to have prostate cancer despite a tPSA > 5.5 ng/mL).

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 tPSA threshold.

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7.7.1.1 Free-to-total PSA %

Lowering the tPSA 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, f/tPSA% can then be used to improve specificity. As the ratio of false positive to true positive biopsies with PSA alone is typically three or four to one, a combined strategy with f/tPSA% 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.

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7.7.1.2 PSA velocity

More formal analysis of PSA dynamics, such as PSA velocity, PSA doubling time or PSA change require at least three or four tPSA measurements separated by several months. For men with tPSA 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.

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7.7.1.3 Prostate Health Index

Criteria for biopsy have been proposed based on PHI thresholds. A given PHI threshold might not be exceeded in a situation where pro2PSA is low and/or free PSA is high, despite a tPSA value greater than 3.0 ng/dL. Therefore, combining a tPSA 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 tPSA specificity with increasing age is not understood.

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7.7.1.4 Repeated total PSA

Given the current focus on tPSA above a given threshold as the criterion for referral or biopsy, men will often be referred as soon as tPSA is above the threshold, regardless of the possibility that that elevation may represent a transient rise from a lower baseline. It has therefore been suggested that elevated tPSA should be confirmed by a repeat test within several weeks. Should the repeat tPSA be below the tPSA threshold, biopsy might be avoided and cancer detection unaffected.

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7.7.2 Evidence

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

7.7.2.1 Free-to-total PSA %

Twelve diagnostic accuracy studies[3][4][5][6][7][8][9][10][11][12][13] were identified that compared the diagnostic performance of the f/tPSA% test with that of total PSA alone in men with tPSA 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.

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These studies found that lowering the f/tPSA% threshold gradually lowered the sensitivity and improved specificity. Eight studies used a f/tPSA% threshold that retained a sensitivity of over 90% compared to tPSA alone.[12][5][9][10][7][11][6] For men with a tPSA less than 5.5 ng/mL, using f/tPSA% 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 tPSA and f/tPSA% during the period 1997– 2006.

Older men will more often have higher tPSA levels (> 4.0 ng/mL), without the presence of prostate cancer. Two studies[14][15] examined the use of f/tPSA% for men aged over 69 years with a tPSA of 4.0–10.0 ng/mL. In one study,[14] a f/tPSA% 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 f/tPSA% 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 between the unnecessary biopsies avoided for each cancer missed.

The use of very low f/tPSA% thresholds improved specificity but compromised sensitivity to an unacceptable degree. For example, the use of f/tPSA % <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]

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7.7.2.2 PSA velocity

One diagnostic accuracy study[16] at risk of bias was identified that compared the diagnostic performance of PSA velocity with that of total PSA alone in men with tPSA 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]

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7.7.2.3 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 tPSA levels above the threshold for biopsy but below 5.5 ng/mL.

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7.7.2.4 Repeated total PSA

Two diagnostic accuracy studies at risk of bias were identified that compared the diagnostic performance of repeat tPSA with that of a single tPSA alone in men with tPSA levels above the threshold for biopsy but below 5.5 ng/mL.[17][18] Both studies found that if the tPSA 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 tPSA 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 tPSA did not fall 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 tPSA 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 tPSA levels that remained elevated, missed 6.0% of cancers and avoided 3.2 unnecessary biopsies for each cancer missed.

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7.7.3 Evidence summary and recommendations

Evidence summary	Level	References
Free-to-total PSA For men with an elevated tPSA less than 4.0 ng/ml, using f/tPSA% thresholds from 25 % to 31% as indications for biopsy can maintain a sensitivity of at least 90%, with 3.8 to 12.5 false positives avoided per cancer missed. For men in a screening population with a tPSA levels less than 4.0 ng/mL but greater than 3.0 ng/mL, using a f/tPSA% threshold of 26% as an indication for biopsy missed 7.4% of cancers, with 12.5 false positives avoided per each cancer missed. For men aged over 69 years with a tPSA of 4.0–10.0 ng/mL and a cancer detection rate of 15%, using a f/tPSA % 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 f/tPSA% improves specificity in men aged under 50 years. Studies that reported f/tPSA% 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 to 4.0 ng/mL reduced sensitivity to an unacceptable degree.	III-2	[16]

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Evidence summary	Level	References
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 In men with an initial tPSA ≥ 3.0 ng/mL, the use of biopsy criteria of failure to normalise tPSA, or failure to reduce tPSA by 30% on repeat tPSA 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 tPSA did not normalise on repeat tPSA, missed 6% of cancers and resulted in a ratio of unnecessary biopsies to missed cancers of 3.20.	III-2	[18], [17]

Evidence-based recommendation	Grade
Offer repeat total PSA to men 50-69 years of age whose total PSA is between 3.0 ng/mL and 5.5 ng/mL and to men >69 years of age whose total PSA is between 3.0 ng/mL and 10.0 ng/mL. If the second total PSA remains > 3.0 ng/mL, offer free-to-total PSA% testing. If the free-to-total PSA% result is <25%, offer prostate biopsy.	**D**

Consensus-based recommendation
Advise men who are not offered or do not accept prostate biopsy that: there is a small chance of missing a significant cancer; total PSA and free-to-total PSA ratio should be measured again within 6 months; and a biopsy should be done if total PSA is > 3ng/mL and free-to-total PSA% is <25%. If at further testing within 6 months these criteria for biopsy are again not met, advise men to return to two-yearly total PSA testing.

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.

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7.7.3.1 Health system implications

7.7.3.1.1 Clinical practice

The use of f/tPSA% is in common usage when tPSA levels are elevated. The f/tPSA% decision thresholds used are either <10%[19] or <25%.

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

7.7.3.1.2 Resourcing

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

The use of f/tPSA% is reimbursable in Australia.

7.7.3.1.3 Barriers to implementation

There are no apparent barriers to the implementation of the recommendations regarding repeat tPSA tests or f/tPSA tests.

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7.7.4 References

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7.7.5 Discussion

Supporting attachments

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7.8.1 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 radical therapy for prostate cancer. Table 2.6 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 from 3.25 months (for freedom from mild fatigue) to 27.69 months (for freedom from severe urinary leakage) when symptoms were considered individually. Therefore, use of mean months of life gained per man diagnosed as an indicator of the balance of benefits and harms is meaningful.

Table 2.6 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
Severe urinary leakage	27.69

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Source: King et al (2012)[1]

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7.8.2 Unresolved issues

7.8.2.1 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 50–69 years of age without a prostate cancer diagnosis or symptoms that might indicate prostate cancer, PSA testing every 2–4 years and a PSA threshold for biopsy of > 3 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 is optimal in balancing the benefits and harms that can flow from PSA testing.

Although the best-quality evidence (results of randomised controlled trials) supports biennial PSA testing of men aged 50 to 69 years, with PSA of ≥ 3 ng/mL as the criterion for further investigation, one model[12] based on the ERSPC results suggests that the criterion of PSA > 95th percentile for age may improve the balance of benefits to harms. It also suggests that balance of benefits to harms may be similar when testing men 40–49 years of age as it is when testing men 50–59 years of age; although much of this benefit could lie with testing in the age-group 45–49 and this has not be adequately assessed in the models.

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.[13] 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.

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7.8.2.2 Australian population PSA reference data

Data from modelling studies suggest that the use of an age-based PSA test criterion for biopsy may achieve higher specificity and avoid unnecessary biopsies. As 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 PSA, most likely the 95th percentile, for age.

Recommendations based on 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.

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7.8.2.3 PSA modalities for improving sensitivity and specificity

It is uncertain how repeat PSA and f/tPSA% work together in avoiding unnecessary biopsies while maintaining sensitivity. Furthermore it is not known how these diagnostic changes impact on clinical outcomes.

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7.8.3 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 much of the information needed for doctors to discourage offers of PSA testing to men with less than 7 years' life expectancy.

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7.8.4 Future research priorities

Future research priories include:

- effects of PSA testing strategies (using different combinations of 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 tPSA and f/tPSA%) used in conjunction with a tPSA threshold of 3.0 ng/mL, especially for men aged 50–69 years and those at high risk.

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8 3 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.

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8.1 Introduction

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8.2 3.1 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 3)**

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8.2.1 Background

Core biopsy of the prostate with histological examination is required to confirm the presence of cancer and, if confirmed, to determine its type, grade and likely extent within the prostate before definitive therapy can be 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.

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8.2.2 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][12][13][14][3][4][15][5][6][16][17][18][19][7][20][21][8][9][10][11][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 meta-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.

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8.2.3 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.

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8.2.4 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 cancers (Gleason score > 6) and all cancers. There was little or no evidence 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.

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8.2.5 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.

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8.2.6 Evidence summary and recommendations

Evidence summary	Level	References
Detection of prostate cancer	I	[12], [13], [1], [14], [4], [15], [5], [6], [16], [17],

Evidence summary	Level	References
Increasing biopsy core number improves cancer yield; as the number of cores increases, the yield increases. A meta-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.		[19], [7], [20], [21], [8], [9], [10], [11], [22], [23]
Detection of prostate cancer There is insufficient evidence to determine if the transperineal approach is superior to the transrectal approach in detecting cancer.	I	[12], [13], [14], [4], [15], [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. There was little or no evidence 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, with no consistent demonstrated increase in events related to core number or biopsy pattern.	II	[1], [4], [5], [6], [7], [9], [10]
Adverse events There is insufficient evidence to determine if the transperineal approach is superior to the transrectal approach in terms of adverse events.	II	[3], [11]

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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
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.

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8.2.6.1 Health system implications

8.2.6.1.1 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.

8.2.6.1.2 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.

8.2.6.1.3 Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

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8.2.8 Discussion

Supporting attachments

View technical report {{{pages}}}   NHMRC Evidence Statement form

8.3 3.2 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 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)**

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8.3.1 Background

A single 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 ratio of free PSA to total PSA (f/tPSA%), 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 in 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 employing imaging techniques are to reduce the number of patients requiring biopsy while minimising the risk of missing significant cancers, and to require fewer biopsies to be taken in men in whom significant lesions are detected (which is appropriate provided that a form of focal therapy is not being contemplated). Thus, the overall aim is to lessen the rate of over diagnosis.

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8.3.2 Evidence

8.3.2.1 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 which reported on the following potential prognostic factors: age, ethnicity, family history of prostate cancer, DRE, total PSA, f/tPSA%, PSA density, PSA velocity[i] and PCA3 at the time of initial biopsy, and histopathological features reported on initial biopsy (high-grade prostatic intra-epithelial neoplasia [PIN] or atypical small acinar proliferation [ASAP][ii]).

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, ftPSA, 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, f/tPSA%, and prostate volume. In the updated NICE systematic review, all the studies found were assessed to have a high risk of bias.

Footnotes: [i] 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 2.4 PSA testing to improve sensitivity after an initial normal total PSA). [ii] 'Atypical small acinar proliferation' and 'atypical glands suspicious for carcinoma' are synonymous classifications.[2][3] 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.

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8.3.2.1.1 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 ($p > 0.05$).[4][5] 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.[6]

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8.3.2.1.2 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)[6] and 0.58 (95% CI 0.23–1.45),[4] relative to men of non-black ethnicity.

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8.3.2.1.3 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)[6] and 0.92 (95% CI 0.50–1.72)[4] in multivariate models.

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8.3.2.1.4 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.[5]

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8.3.2.1.5 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 a PSA of > 10 relative to < 4 ng/mL (p = 0.18).[5] The other study did not report multivariate-adjusted results for PSA.[6]

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8.3.2.1.6 Ratio of free to total PSA

The NICE review[1] found eight studies of the relationship of f/tPSA% 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 f/tPSA%. 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 f/tPSA%. In each case the OR was < 1 for the higher category relative to the lower category, but none was statistically significant. Sensitivity and specificity were not consistent for similar f/tPSA% 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 f/tPSA% with risk of prostate cancer at re-biopsy,[6] but it did not report multivariate-adjusted results.

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8.3.2.1.7 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,[6] but it did not report multivariate-adjusted results.

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8.3.2.1.8 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 of PSA velocity with risk of prostate cancer at re-biopsy.

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8.3.2.1.9 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).[6]

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8.3.2.1.10 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 to 3.2. Only one of these reported an OR < 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)[6] and 1.25 (p = 0.5).[5]

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8.3.2.1.11 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.

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8.3.2.1.12 DNA methylation

The updated NICE systematic review found one study[5] 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 64%.

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8.3.2.2 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[7][8] and one randomised controlled trial[9] of enhanced ultrasound.

The other studies were cohort studies, case series studies or comparative studies.[1] These 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] was updated by the Guidelines' Expert Advisory Panel (see *Technical report*). The updated NICE systematic review was restricted to studies that directly compared different post negative biopsy investigations, i.e. sequential sampling studies or randomised controlled trials (level II evidence).

The NICE systematic review included case series (level IV evidence) as well as comparative studies.[1] NICE assessed the risk of bias using the QUADAS-2 checklist.[10] 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] In the updated NICE systematic review, the literature search was restricted to studies that directly compared different investigations undertaken post negative biopsy (i.e. sequential sampling studies or randomised controlled trials; level II evidence). Eight additional level II evidence sequential sampling studies were found.[11][12][13][14][15][16][17][18] All eight update studies were asssessed to be at moderate risk of bias using a modified QUADAS-2 quality appraisal tool.[11][12][13][14][15][16][17][18] The quality assessment criteria, including those for assessing risk of bias, are described in the Technical Report.

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8.3.2.2.1 Multiparametric MRI targeted biopsy

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. [1]

The updated NICE systematic review studies showed that compared with standard biopsies (more than 20 cores), adding multiparametric MRI targeted biopsies to the standard biopsies improved cancer detection rates by 0–5.1 percentage points.[11][19][12][13][20][14][21][15][16][22][17] Compared with 12 core biopsy protocols adding multiparametric MRI (T2W+DCE, 3T MRI or unspecified multiparametric MRI) targeted biopsies improved cancer detection rates by 6.4–10.2 percentage points.

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8.3.2.2.2 Enhanced ultrasound targeted biopsy

Studies included in the NICE systematic review found that adding 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]

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8.3.2.2.3 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: 8.8% of men undergoing transrectal saturation biopsy and 23.4% of men undergoing transperineal biopsy.

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8.3.2.2.4 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.[18]

8.3.2.2.5 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 to benign.[1]

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8.3.3 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% to 10% greater risk of prostate cancer at re-biopsy.	III-2, III-3	[1], [6], [4], [5]
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.	III-2, III-3	[1], [6], [4]
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.	III-2, III-3	[1], [6], [4]

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Evidence summary	Level	References
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.	III-2, III-3	[1], [5]
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.	III-2, III-3	[1], [6], [5]
Ratio of free to total PSA There is inconsistent evidence that a higher f/tPSA% at an initial negative prostate biopsy predicts a lower risk of prostate cancer at re-biopsy.	III-2, III-3	[1], [6]
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.	III-2, III-3	[1], [6]
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.	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.	III-2, III-3	[1], [6]
High-grade PIN There is moderately consistent evidence that high-grade PIN at an initial negative biopsy predicts, but with low diagnostic accuracy, a higher risk of prostate cancer at re-biopsy.	III-2, III-3	[1], [6], [5]
PCA3	III-2, III-3	[1]

Evidence summary	Level	References
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.		
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.	III-2, III-3	[5]
Multiparametric MRI-targeted biopsy 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. A single study from the updated NICE systematic review showed that a repeat saturation biopsy detected 35.9% of cancers. Adding 3–4 multiparametric MRI targeted biopsies increased the cancer detection rate by an additional 5.1 percentage points.	II, IV	[11], [19], [12], [13], [20], [14], [21], [15], [16], [22], [17], [1]
Enhanced ultrasound-targeted biopsy Studies included in the NICE systematic review found that adding 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.	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: 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.	II, IV	[18], [1]

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Evidence summary	Level	References
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.		
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 to 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 intra-epithelial 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 up. Monitor more closely for those with abnormal findings on pre-biopsy digital rectal examination, and for 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
Advise men whose initial biopsy is negative for prostate cancer and are at average risk for prostate cancer and have a life expectancy of less than 7 years due to age or illness, that no further action is recommended unless they develop symptoms that suggest prostate cancer.	**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 intra-epithelial neoplasia on initial biopsy.	**D**

Practice point
✣ Multiparametric MRI should be used only in centres with experienced radiologists appropriately trained in the use of multi-parametric MRI to aid urologists in the management of individual patients.   ✣ Clinicians and other staff performing multiparametric MRI should do so in accordance with appropriate standards and guidelines for its use.   ✣ 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.   ✣ 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.

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8.3.3.1 Health system implications

8.3.3.1.1 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.

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8.3.3.1.2 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.

8.3.3.1.3 Barriers to implementation

At present, facilities for performing multiparametric MRI and expertise in its interpretation are limited to major metropolitan centres. There is currently no Medicare Item number for multiparametric MRI in assessment of the prostate. The cost of this imaging procedure may be a deterrent for some men.

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8.3.4 Reference

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8.3.5 Discussion

Supporting attachments

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8.4 Discussion

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8.4.1 Discussion

8.4.1.1 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. Cost-benefit analysis would be needed to identify the appropriate role of this technology, given that it cannot identify all prostate tumours, including all clinically significant tumours.

9 4 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 9.1)

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)

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9.1 Background

Active surveillance 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, to avoid treatment-related effects that may reduce quality of life. Definitive therapy 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 multi-parametric prostate magnetic resonance imaging (MRI). Evidence is lacking 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.

9.2 Evidence

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

Three cohort studies[1][2][3] reported mortality and quality of life outcomes in men who underwent either surveillance or immediate treatment. These studies demonstrated excellent prostate cancer-specific survival rates for men with prostate cancer managed by active surveillance. In a prospective cohort study[2] in men with PSA ≤ 20 ng/mL, T1c prostate cancer, 1–2 cores involved and Gleason score ≤ 6, no difference in prostate cancer-specific mortality was demonstrated between the immediate treatment and active surveillance groups after 2.8 to 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, slightly higher prostate cancer-specific mortality 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). Rates of cancer death were low, both overall (13.6%) and among those men with Gleason score ≤ 6, PSA ≤ 20 ng/mL and 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 reported four analyses from three studies,[5][6][7] all of which reported results with end points of cessation of active surveillance and did not report overall survival, prostate cancer-specific mortality or quality of life. Factors analysed included PSA velocity, PSA doubling time, PSA level at diagnosis, PSA density, free-to-total PSA ratio, 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.

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9.2.2 Active surveillance protocols

Three cohort studies were identified that compared immediate treatment with delayed treatment.[1][2][3] All were assessed to be of low quality. 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).

9.3 Evidence summary and recommendations

Evidence summary	Level	References
Three cohort studies reported excellent prostate cancer-specific survivals for men with prostate cancer managed by active surveillance. In men with early prostate cancer with PSA ≤ 20 ng/mL, clinical stage T1-2, and Gleason score ≤ 6, active surveillance was associated with a similarly low risk of death due to prostate cancer as immediate definitive treatment.	III-2	[1], [2], [3]
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 ratio, 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 ng/mL/year predicted progression from active surveillance to definitive treatment (p < 0.001) in one study.	III-2	[5], [6], [7], [8], [2], [1], [3]

Evidence-based recommendation	Grade
Offer active surveillance to men with prostate cancer who meet all the following criteria: ■ PSA ≤ 20 ng/mL ■ clinical stage T1-2 ■ Gleason score 6.	**C**

Consensus-based recommendation
Consider offering active surveillance to men with PSA ≤ 10 ng/mL, clinical stage T1-2a prostate cancer and Gleason score ≤(3+4=7) if pattern 4 component is < 10% after pathological review. For patients with PSA 10-20 ng/ml or T2B or C disease, consider definitive treatment or repeat biopsy if active surveillance is strongly preferred by the patient.

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Consensus-based recommendation

Consider offering active surveillance to younger men (< 60 years of age) with PSA ≤ 10 ng/mL, clinical stage T1-2a and Gleason score ≤(3+4=7) if pattern 4 component is < 10%, provided that the patient understands that treatment in these circumstances may be delayed rather than avoided.

For younger men (< 60 years of age) with PSA 10-20 ng/ml or T2B or C disease, consider definitive treatment or repeat biopsy if active surveillance is strongly preferred by the patient.

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.

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> **Practice point**
>
> ⁺ Advise men with prostate cancer who have PSA ≤ 20 ng/mL, clinical stage T1-2, and Gleason score 6 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.

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9.3.1 Health system implications

9.3.1.1 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.

9.3.1.2 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 2) 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.

9.3.1.3 Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

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9.4 References

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9.5 Discussion

Supporting attachments

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9.1 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 9.1)

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)

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9.1.1 Background

Active surveillance 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, to avoid treatment-related effects that may reduce quality of life. Definitive therapy 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 multi-parametric prostate magnetic resonance imaging (MRI). Evidence is lacking 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.

9.1.2 Evidence

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

Three cohort studies[1][2][3] reported mortality and quality of life outcomes in men who underwent either surveillance or immediate treatment. These studies demonstrated excellent prostate cancer-specific survival rates for men with prostate cancer managed by active surveillance. In a prospective cohort study[2] in men with PSA ≤ 20 ng/mL, T1c prostate cancer, 1–2 cores involved and Gleason score ≤ 6, no difference in prostate cancer-specific mortality was demonstrated between the immediate treatment and active surveillance groups after 2.8 to 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, slightly higher prostate cancer-specific mortality 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). Rates of cancer death were low, both overall (13.6%) and among those men with Gleason score ≤ 6, PSA ≤ 20 ng/mL and 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 reported four analyses from three studies,[5][6][7] all of which reported results with end points of cessation of active surveillance and did not report overall survival, prostate cancer-specific mortality or quality of life. Factors analysed included PSA velocity, PSA doubling time, PSA level at diagnosis, PSA density, free-to-total PSA ratio, 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.

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9.1.2.2 Active surveillance protocols

Three cohort studies were identified that compared immediate treatment with delayed treatment.[1][2][3] All were assessed to be of low quality. 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).

9.1.3 Evidence summary and recommendations

Evidence summary	Level	References
Three cohort studies reported excellent prostate cancer-specific survivals for men with prostate cancer managed by active surveillance. In men with early prostate cancer with PSA ≤ 20 ng/mL, clinical stage T1-2, and Gleason score ≤ 6, active surveillance was associated with a similarly low risk of death due to prostate cancer as immediate definitive treatment.	III-2	[1], [2], [3]
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 ratio, 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 ng/mL/year predicted progression from active surveillance to definitive treatment (p < 0.001) in one study.	III-2	[5], [6], [7], [8], [2], [1], [3]

Evidence-based recommendation	Grade
Offer active surveillance to men with prostate cancer who meet all the following criteria: ■ PSA ≤ 20 ng/mL ■ clinical stage T1-2	C

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Evidence-based recommendation	Grade
■ Gleason score 6.	

Consensus-based recommendation

Consider offering active surveillance to men with PSA ≤ 10 ng/mL, clinical stage T1-2a prostate cancer and Gleason score ≤(3+4=7) if pattern 4 component is < 10% after pathological review.

For patients with PSA 10-20 ng/ml or T2B or C disease, consider definitive treatment or repeat biopsy if active surveillance is strongly preferred by the patient.

Consensus-based recommendation

Consider offering active surveillance to younger men (< 60 years of age) with PSA ≤ 10 ng/mL, clinical stage T1-2a and Gleason score ≤(3+4=7) if pattern 4 component is < 10%, provided that the patient understands that treatment in these circumstances may be delayed rather than avoided.

For younger men (< 60 years of age) with PSA 10-20 ng/ml or T2B or C disease, consider definitive treatment or repeat biopsy if active surveillance is strongly preferred by the patient.

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 prostate cancer who have PSA ≤ 20 ng/mL, clinical stage T1-2, and Gleason score 6 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.

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9.1.3.1 Health system implications

9.1.3.1.1 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.

9.1.3.1.2 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 2) 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.

9.1.3.1.3 Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

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9.1.4 References

1. ↑ [1.0] [1.1] [1.2] [1.3] [1.4] Holmström B, Holmberg E, Egevad L, Adolfsson J, Johansson JE, Hugosson J, et al. *Outcome of primary versus deferred radical prostatectomy in the National Prostate Cancer Register of Sweden Follow-Up Study.* J Urol 2010 Oct;184(4):1322-7 Available from: http://www.ncbi.nlm.nih.gov /pubmed/20723940.
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9.1.5 Discussion

Supporting attachments

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9.2 Discussion

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9.2.1 Discussion

9.2.1.1 Unresolved issues

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

- difficulty in estimating life expectancy.
- the safety of active surveillance in men diagnosed with Gleason 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.

The optimal criteria for watchful waiting have not been identified. No studies published in English have compared the outcomes of watchful waiting with those of immediate definitive treatment in men who have prostate cancer that is sufficiently advanced to be unlikely to be curable by either radical prostatectomy or radical radiotherapy.

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. A study published after the systematic reviews were completed for this guideline 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.

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9.2.1.2 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[2] (Germany)
- 'Prostate Testing for Cancer and Treatment' (ProtecT) trial[3][4] (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.[5][6]

9.2.1.3 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 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.

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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9.2.2 References

1. ↑ Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. *Radical prostatectomy versus watchful waiting in early prostate cancer.* N Engl J Med 2011 May 5;364(18):1708-17 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21542742.
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10 5 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 9.2)

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)

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10.1 Background

Watchful waiting is a conservative strategy for managing asymptomatic prostate cancer. 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 potential 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 fewer than 10 years (for reasons other than prostate cancer) if they survive beyond 10 years.

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. Symptoms assessed may include pain indicative of bone metastases, urinary or renal symptoms indicative of obstruction, lower limb swelling indicative of pelvic lymphadenopathy or venous thrombosis, lower limb weakness indicative of spinal cord compression, changes in bowel habit indicative of rectal compression, and constitutional symptoms (fatigue, anorexia, nausea). Physical assessment may include a digital rectal examination of the prostate to assess its local extent and progression. Laboratory testing may include serum for PSA to assess the rate of progression, for creatinine to assess renal function, for alkaline phosphatase to help detect bone metastases, and a full blood count to assess marrow involvement.

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10.2 Evidence

10.2.1 Criteria for selecting watchful waiting

Two randomised controlled trials[1][2] were identified that reported prostate cancer-specific mortality and other relevant outcomes in men with early stage (T1-2NxM0) prostate cancer randomised to immediate radical prostatectomy or to watchful waiting. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report. The first trial (SPCG-4)[1] randomised 695 men with early stage, low 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:

- all-cause mortality (hazard ratio [HR] 0.75; confidence interval [CI] 0.61–0.92)
- prostate cancer-specific mortality (relative risk ratio [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 Gleason score < 7 or a WHO cancer grade 1). The impact of radical prostatectomy appeared to be limited to, or greater for, men (less 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 (PIVOT){Wilt, 2012 33 /id} 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 therapy. Of those randomised to watchful waiting, 10.1% had RP and 20.4% had definitive therapy.

Intention-to-treat analysis done at median 10.0 years of follow-up favoured radical prostatectomy for development of bony metastases (HR 0.40; CI 0.22 to 0.70) and showed non-statistically 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 is higher all-causes and prostate cancer mortality and a higher rate of development of distant metastases in men randomised to watchful waiting than in men randomised to radical prostatectomy. They were not consistent,

however, 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 all-cause mortality and prostate cancer-specific mortality, and in rate of development of distant metastases, in men with low risk cancer (PSA < 10 ng/mL or Gleason score < 7 or a 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 RP. 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 (at mean of 4.1 years[3] 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 urinary incontinence and distress and erectile dysfunction and 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.

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10.2.2 Watchful waiting protocols

No high-quality studies (randomised controlled trials) were found that tested or compared follow-up schedules or strategies for watchful waiting. In the absence of high quality direct evidence, a useful starting point could be the schedules used for the control groups in randomised clinical trials comparing various active treatments versus watchful waiting in three different clinical settings: 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 both with respect to frequency and number and nature of investigations than would be desirable for clinical practice.

In the absence of relevant published evidence on which to base watchful waiting protocols, we adapted NICE 2014[8] recommendations for managing localised prostate cancer and managing relapse after definitive treatment, which were informed by available evidence and represent current international expert consensus.

10.3 Evidence summary and recommendations

Evidence summary	Level	References
The studies were inconsistent in patient selection and in their findings on effects of age and risk of cancer progression (as assessed at diagnosis) on observed differences in all-cause mortality, prostate cancer-specific mortality and occurrence of 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, 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]

Evidence-based recommendation	Grade
Advise men with potentially curable prostate cancer considering watchful waiting that their risk of developing more advanced prostate cancer and dying from it will be higher with watchful waiting than with immediate definitive treatment but that, in the medium- to long-term, watchful waiting is unlikely to diminish their wellbeing and quality of life.	C

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; or ✝ 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 (2014){National Collaborating Centre for Cancer, 2014 11 /id}

Consensus-based recommendation

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 further clinical investigations).

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.

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10.3.1 Health system implications

10.3.1.1 Clinical practice

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

10.3.1.2 Resourcing

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

10.3.1.3 Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

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10.4 References

1. ↑ [1.0] [1.1] [1.2] [1.3] [1.4] Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. *Radical prostatectomy versus watchful waiting in early prostate cancer.* N Engl J Med 2011 May 5;364(18):1708-17 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21542742.
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7. ↑ Studer UE, Whelan P, Wimpissinger F, Casselman J, de Reijke TM, Knönagel H, et al. *Differences in Time to Disease Progression Do Not Predict for Cancer-specific Survival in Patients Receiving Immediate or Deferred Androgen-deprivation Therapy for Prostate Cancer: Final Results of EORTC Randomized Trial 30891 with 12 Years of Follow-up.* Eur Urol 2013 Jul 24 Available from: http://www.ncbi.nlm.nih.gov /pubmed/23932338.
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10.5 Discussion

Supporting attachments

View technical report {{{pages}}}   NHMRC Evidence Statement form

10.1 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 9.2)

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)

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The decision to undertake watchful waiting is made in agreement with the patient after explaining the available options and discussing their potential 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).

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10.1.2 Evidence

10.1.2.1 Criteria for selecting watchful waiting

Two randomised controlled trials[1][2] were identified that reported prostate cancer-specific mortality and other relevant outcomes in men with early stage (T1-2NxM0) prostate cancer randomised to immediate radical prostatectomy or to watchful waiting. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report. The first trial (SPCG-4)[1] randomised 695 men with early stage, low 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:

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

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10.1.2.2 Watchful waiting protocols

No high-quality studies (randomised controlled trials) were found that tested or compared follow-up schedules or strategies for watchful waiting. In the absence of high quality direct evidence, a useful starting point could be the schedules used for the control groups in randomised clinical trials comparing various active treatments versus watchful waiting in three different clinical settings: 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 both with respect to frequency and number and nature of investigations than would be desirable for clinical practice.

In the absence of relevant published evidence on which to base watchful waiting protocols, we adapted NICE 2014[8] recommendations for managing localised prostate cancer and managing relapse after definitive treatment, which were informed by available evidence and represent current international expert consensus.

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10.1.3 Evidence summary and recommendations

Evidence summary	Level	References
The studies were inconsistent in patient selection and in their findings on effects of age and risk of cancer progression (as assessed at diagnosis) on observed differences in all-cause mortality, prostate cancer-specific mortality and occurrence of 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, 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]

Evidence-based recommendation	Grade
Advise men with potentially curable prostate cancer considering watchful waiting that their risk of developing more advanced prostate cancer and dying from it will be higher with watchful waiting than with immediate definitive treatment but that, in the medium- to long-term, watchful waiting is unlikely to diminish their wellbeing and quality of life.	C

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; or ✚ choose not to accept potentially curative therapy when it is offered to them.

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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 (2014){National Collaborating Centre for Cancer, 2014 11 /id}

Consensus-based recommendation

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 further clinical investigations).

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.

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10.1.3.1 Health system implications

10.1.3.1.1 Clinical practice

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

10.1.3.1.2 Resourcing

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

10.1.3.1.3 Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

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10.1.5 Discussion

Supporting attachments

View technical report {{{pages}}}   NHMRC Evidence Statement form

10.2 Discussion

10.2.1 Discussion

10.2.1.1 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).

11 6 Sociocultural aspects of PSA Testing in Australia

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11.1 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] It is important to identify their needs and decrease barriers to accessing screening programs and appropriate treatment services in order to reduce existing disparities.

11.2 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 males in the least disadvantaged quintile (171 per 100,000) and lowest in

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the most disadvantaged quintile (126 per 100,000).[3] Prostate cancer incidence rates in the second, third and fourth quintiles were, however, 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 males in the least disadvantaged quintile had a higher 5-year survival rate than males 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 three years after a prostate cancer diagnosis (RR 1.34; 95% CI 1.10–1.64).[5] The risk of dying within three 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]

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11.3 Accessibility

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]

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11.4 Aboriginal and Torres Strait Islander men

Aboriginal and Torres Strait Islander men in Australia were 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.[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 five years following a diagnosis.[17]

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11.5 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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11.6 References

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11.1 Appendix 1 Guideline development process

11.1.1 Introduction

The Prostate Cancer Foundation of Australia (PCFA) initiated the process to develop 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. A decision to proceed following NHMRC agreement to consider the guideline was taken in November 2012. To better describe the scope of the guideline, the title was changed to Clinical practice Guideline 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.

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11.1.2 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 multi-disciplinary 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 men affected by prostate cancer were represented to form a multi-disciplinary group. In addition, 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 designated Project Steering Committee. The 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

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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 questions to address identified clinical needs. The questions were allocated to specific Guidelines Expert Advisory Panel members to be lead authors of a question in their areas of expertise. Each lead author team was able to co-opt additional experts, that 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).

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11.1.3 Steps in preparing clinical practice guidelines to NHMRC criteria

For every question the following steps were followed.

1. Developing a structured clinical question (PICO question)

2. Search for existing relevant guidelines and systematic reviews

3. Process if relevant clinical practice guideline 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	Critical appraisal and data extraction of each new included article
Screening of literature results against pre-defined inclusion and exclusion criteria	Update evidence table of evidence review of existing guideline with new literature update

	results
Critical appraisal and data extraction of each included article	

4. Summary of the relevant data

5. Assessment 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. Assessing the body of evidence and formulate recommendations

7. Writing the content narrative

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11.1.3.1 Developing a structured clinical question

A wide range of questions was proposed for research. The questions focussed 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.

11.1.3.2 Search for existing relevant guidelines and systematic reviews

For each PICO question, the National Guideline Clearinghouse (http://guideline.gov/) the Guidelines Resource Centre (www.cancerview.ca) 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 9.1.

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 Developing a systematic search strategy; 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.

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11.1.3.3 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.

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11.1.3.4 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 .

- 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.

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11.1.3.5 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 1 reviewer. 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.

11.1.3.6 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).

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11.1.3.7 Guideline adaption for PICO questions 8.1, 8.2 and 9.1

For clinical questions 8.1, 8.2, and 9.1, 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 ie 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 9.1 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 Guideline adaption for PICO questions 8.1, 8.2 and 9.1). 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.

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11.1.3.8 Meta-analysis for clinical question 3

For clinical question 3, 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.

11.1.3.9 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 (see Technical report). Levels of evidence are outlined 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

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11.1.3.10 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 in regard to 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	Recommendation Grade			
	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

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11.1.3.11 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.

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11.1.4 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, 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.

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11.1.5 Public consultation

Draft text included and to be modified as necessary after public consultation

A complete draft of the guideline was sent out for public consultation in Australia 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 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 and other relevant stakeholders.

All feedback on the draft received during the consultation period in Australia will be 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 will be assessed by the methodologist team against the systematic review protocol. If a submitted paper meets the inclusion criteria, it will be assessed for quality by two assessors and the data will be extracted. The evidence tables, systematic review report, content narrative, evidence statements and recommendations will then be updated as a result. Another face-to-face meeting is organised amongst the Expert Advisory Panel to review all public consultation comments

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and the amended content. Subsequent changes to the draft will be agreed by consensus, based on consideration of the evidence. The same consensus process that was followed during the face to face Expert Advisory Panel meeting prior to public consultation will be followed again. All changes resulting from the public consultation submission reviews will be documented and made accessible once the guidelines are published. A final independent review of experts in their fields will be conducted before the final draft is 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.

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11.1.6 Organisations formally endorsed the guidelines

TO BE CONFIRMED FOLLOWING COMPLETION OF THE GUIDELINES

The following medical colleges and professional bodies will be 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).

11.1.7 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 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.

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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 HealthInSite, 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. QStream, a clinically proven online education method that was originally developed by Harvard Medical School, will be used (http://qstream.com/company/brain-science). 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.

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11.1.8 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 for this guidelines to be updated after 3 years.

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11.2 Appendix 2 Committee members and contributors

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11.3 Appendix 3 List of clinical questions

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11.4 Appendix 4 TNM classification of prostate tumours

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11.5 Appendix 5 Abbreviations and glossary

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11.6 Appendix 6 Conflict of interest register

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