PSA Testing Clinical Practice Guidelines

Perth CCWA GP Update August 2016

Jon Emery
Herman Professor of Primary Care Cancer Research
Victorian Comprehensive Cancer Centre
• 33% of male cancers
• 1 in 7 risk of diagnosis by age 75
• 2\textsuperscript{nd} cause of cancer deaths in men (6\textsuperscript{th} all male deaths)
• 92% 5 year survival
• By 2017 1.6% of male population (185,000) men living with prostate cancer
Clinical practice guidelines PSA Testing and Early Management of Test-Detected Prostate Cancer.
A plethora of guidelines about PSA testing

Guidelines for preventive activities in general practice 8th edition

9.8 Prostate cancer

Screening for prostate cancer is not recommended unless:
1. the man specifically asks for it; and
2. he is fully counselled on the pros and cons.

American Urological Association (AUA) Guideline

EARLY DETECTION OF PROSTATE CANCER: AUA GUIDELINE

H. Ballentine Carter, Peter C. Albertsen, Michael J. Barry, Ruth Etzioni, Stephen J. Freedland, Kirsten Lynn Greene, Lars Holmberg, Philip Kantoff, Badrinath R. Konety, Mohammad Hassan Murad, David F. Penson and Anthony L. Zietman

U.S. Preventive Services Task Force

Guidelines on Prostate Cancer

N. Mottet (Chair), J. Bellmunt, E. Briers (Patient Representative), R.C.N. van den Bergh (Guidelines Associate), M. Bolla, N.J. van Casteren (Guidelines Associate), P. Cornford, S. Culine, S. Joniau, T. Lam, M.D. Mason, V. Matveev, H. van der Poel, T.H. van der Kwast, O. Rouvière, T. Wiegel

Urological Society of Australia and New Zealand

PSA Guidelines
Prostate cancer screening
PSA TESTING AND EARLY MANAGEMENT OF TEST-DETECTED PROSTATE CANCER

CLINICAL PRACTICE GUIDELINES

A guideline for health professionals
Ongoing source of confusion....
• Key recommendations about PSA testing
• Rationale and evidence
• Implications for practice
PSA testing and effect on prostate cancer deaths: Cochrane review

D Ilic et al Cochrane review 2013
Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up


Manuscript received March 17, 2011; revised November 8, 2011; accepted November 9, 2011.

Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

US PLCO trial results at 13 years

Andriole et al JNCI 2012 (n = 76,685 men randomised.)

Figure 3. Cumulative deaths from prostate cancer in the intervention and control arms from year 1 to year 13. C = control arm; I = intervention arm; PY = person-years.
European ERSPC trial results at 13 years

RR = 0.79 (95% CI = 0.69-0.91 p = 0.001)

Schroder et al Lancet 2014 (n = 162,388 men randomised)
Greater weight given to results of ERSPC trial

• PLCO trial
  – 44% had PSA test in 3 years before trial
  – 52% men in control had PSA in period of last test for intervention group (cf 30.7% in ERSPC)
  – Lower biopsy rates for PSA +ve (PLCO 41% vs ERSPC 86%)

• ERSPC trial
  – Pattern of differences in mortality beginning at 7 years
  – Internal consistency in results between centres
## Summary of ERSPC results for 11 and 13 years follow-up

<table>
<thead>
<tr>
<th>Results</th>
<th>Results up to 11 years of follow-up&lt;sup&gt;23&lt;/sup&gt;</th>
<th>Results up to 13 years of follow-up&lt;sup&gt;33&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (years)</td>
<td>11.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Number of prostate cancer deaths in intervention group</td>
<td>299</td>
<td>355</td>
</tr>
<tr>
<td>Number of prostate cancer deaths in control group</td>
<td>462</td>
<td>545</td>
</tr>
<tr>
<td>Relative risk of death from prostate cancer – intervention group relative to control group</td>
<td>0.79 (95% CI 0.68–0.91)</td>
<td>0.79 (95% CI 0.69–0.91)</td>
</tr>
<tr>
<td>Absolute difference in risk of death from prostate cancer between intervention group and control group</td>
<td>-0.10 per 1,000 person years</td>
<td>-0.11 per 1,000 person years</td>
</tr>
<tr>
<td>Number needed to invite (NNI) to avert one prostate cancer death</td>
<td>1,055</td>
<td>781</td>
</tr>
<tr>
<td>Number needed to detect (NND) to avert one prostate cancer death</td>
<td>37</td>
<td>27</td>
</tr>
</tbody>
</table>

Sources: Schroder et al (2012)<sup>23</sup>, Schroder et al (2014)<sup>33</sup>

Clinical practice guidelines PSA Testing and Early Management of Test-Detected Prostate Cancer.
Evidence about metastatic prostate cancer

- PLCO and ERSPC showed lower risk of metastatic prostate cancer at diagnosis in intervention group

- PLCO: RR 0.87 (95% CI 0.66-1.14)
- ERSPC: RR 0.50 (95% CI 0.41-0.62)
• Men aged 55-69 yrs
• 4 yearly except one centre (2 yearly in Goteborg)
• PSA >3.0 ng/mL without DRE as criterion to refer for biopsy
• End testing 70-75 yrs
## Models of different testing protocols: 4 yearly vs 2 yearly

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Protocol specifications</th>
<th>Modelled protocol outcomes*</th>
<th>Change from less to more aggressive protocol in each pair</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSA testing age (years)</td>
<td>≥ 1 false positive (%)</td>
<td>Over-diagnosis (%)</td>
</tr>
<tr>
<td>Outcomes of testing in men aged 55-69 and 50-69 years¹</td>
<td>PSA testing interval</td>
<td>55-69</td>
<td>≥ 3.0 ng/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-69</td>
<td>≥ 3.0 ng/mL</td>
</tr>
</tbody>
</table>

¹ PSA testing interval: 2 years for men aged 50-69 years.
Recommendation #1: testing average risk men aged 50-69

Evidence-based recommendation
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.
Recommendation #2 and #3: PSA in older men or with reduced life expectancy

Consensus recommendation
Advise men 70 years or older who have been informed of the benefits and harms of testing and who wish to start or continue regular testing that the harms of PSA testing may be greater than the benefits of testing in men of their age.

Evidence-based recommendation
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.
Role of the digital rectal examination?
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)³⁹
Evidence-based recommendation
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.

Remains important part of assessment by urologist as part of assessment and consideration for prostate biopsy
Using PSA test to inform subsequent PSA testing

- PSA as a screening test to diagnose prostate cancer
- PSA as a test to predict risk of future prostate cancer
### Risk of prostate cancer death according to PSA result in your 40s

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Length of follow-up (years)</th>
<th>Reference PSA level</th>
<th>Compared PSA level</th>
<th>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)</th>
<th>Relative risk of prostate cancer death to the end of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orsted et al, 2012</td>
<td>&lt; 45</td>
<td>10</td>
<td>≤ 1.0 ng/mL</td>
<td>Cumulative risk % of prostate cancer death to the end of follow-up</td>
<td>&gt; 1.0–2.0 ng/mL</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; 2.0–3.0 ng/mL</td>
<td>1.2</td>
</tr>
<tr>
<td>Vickers et al, 2013</td>
<td>37.5–42.5</td>
<td>20</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orsted et al, 2012</td>
<td>45–49</td>
<td>10</td>
<td>≤ 1.0 ng/mL</td>
<td></td>
<td>&gt; 1.0–2.0 ng/mL</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; 2.0–3.0 ng/mL</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>Highest quarter, ≥ 1.1 ng/mL</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Highest tenth, ≥ 1.6 ng/mL</td>
<td>0.66</td>
</tr>
<tr>
<td>Vickers et al, 2013</td>
<td>45–49</td>
<td>20</td>
<td>Lowest quarter, ≤ 0.42 ng/mL</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Highest quarter, ≥ 1.1 ng/mL</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Highest tenth, ≥ 1.6 ng/mL</td>
<td>2.18</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td>Highest quarter, ≥ 1.1 ng/mL</td>
<td>2.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Highest tenth, ≥ 1.6 ng/mL</td>
<td>4.62</td>
</tr>
</tbody>
</table>

- >75\textsuperscript{th} centile PSA aged 45 RR for prostate cancer death = 3.9
- >90\textsuperscript{th} centile PSA aged 45 RR for prostate cancer death = 9.2
Recommendation #5 PSA in men 45-50 as a risk predictor

**Consensus recommendation**
For men **younger than 50 years** who are concerned about their risk for prostate cancer, have been informed of the benefits and harms of testing, and who wish to undergo regular testing for prostate cancer, offer testing every 2 years from age 45 to age 69 years.

If initial PSA is at or **below the 75th percentile** for age, advise no further testing until age 50.

If initial PSA is **above the 75th percentile** for age, but at or below the 95th percentile for age, reconfirm the offer of testing every 2 years.

If a PSA test result before age 50 years is **greater than the 95th percentile** for age, offer further investigation.

Offer testing from age 50 years according to the protocol for all other men who are at average risk of prostate cancer.
PSA testing in men with a family history of prostate cancer

<table>
<thead>
<tr>
<th>Relative risk of prostate cancer</th>
<th>Mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 40</td>
</tr>
<tr>
<td></td>
<td>(mortality at age 50 minus mortality at age 40)</td>
</tr>
<tr>
<td>1.0 (average risk)</td>
<td>2.3</td>
</tr>
<tr>
<td>2.0</td>
<td>4.7</td>
</tr>
<tr>
<td>2.5</td>
<td>5.8</td>
</tr>
<tr>
<td>3.0</td>
<td>7.0</td>
</tr>
<tr>
<td>3.5</td>
<td>8.2</td>
</tr>
<tr>
<td>4.0</td>
<td>9.3</td>
</tr>
<tr>
<td>5.0</td>
<td>11.7</td>
</tr>
<tr>
<td>6.0</td>
<td>14.0</td>
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<tr>
<td>7.0</td>
<td>16.4</td>
</tr>
<tr>
<td>8.0</td>
<td>18.7</td>
</tr>
<tr>
<td>9.0</td>
<td>21.1</td>
</tr>
<tr>
<td>10.0</td>
<td>23.4</td>
</tr>
</tbody>
</table>
Recommendation #6: men with a family history of prostate cancer:

Consensus recommendation
For men whose risk of prostate cancer is estimated to be at least 2.5–3 times higher than average (e.g. a brother with prostate cancer, particularly if <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 (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.
What to do with a PSA >3.0?

- Single PSA >3.0: PPV = 20-25%
- Day-to-day variability in PSA level by 15%

- How to increase PPV and reduce prostate biopsy rate?
Recommendations #7 and 8: repeat testing and free-to-total PSA

**Evidence-based recommendation**
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.

**Consensus recommendation**
Offer prostate biopsy:
— if repeat total PSA is greater than 5.5 ng/mL, regardless of free-to-total PSA percentage
— if repeat total PSA is greater than 3.0 ng/mL and less than or equal to 5.5 ng/mL and free-to-total PSA <25%
Measurement of **PSA velocity** is not recommended to increase specificity of a total PSA test result of 3.0 ng/mL or greater.

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.

Additional recommendation confirming no clear benefit to increase **sensitivity** to detect prostate cancer
Supporting men to decide about PSA testing

- **Decision aids:**
  - Improve men’s knowledge about harms and benefits of PSA testing
  - Reduce decisional conflict/distress
  - Increase men’s satisfaction with their decision
**Evidence-based recommendation**
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.

- **Do not just add a PSA onto a list of other tests** without a discussion
- Need to find time to discuss the test and use a decision aid as part of that discussion
- Recommend use of NHMRC fact sheet
Possible benefit of PSA testing

- For every 1000 men tested, 2 men will avoid death from prostate cancer before 85 years of age because of PSA testing¹. This benefit might be greater for men at high risk of prostate cancer, such as those with a strong family history of the disease.
- For every 1000 men tested, 2 men will avoid metastatic prostate cancer before 85 years of age because of PSA testing².

Expected harms of PSA testing

**False-positive results:**
- For every 1000 men tested:
  - 87 men who do not have prostate cancer will have a false positive PSA test that will lead to a biopsy¹.
  - 28 men will experience a side effect from the biopsy that they consider to be a moderate/major problem that may require healthcare, and 1 will require hospitalisation³.

**Overdiagnosis:**
- For every 1000 men tested, 28 men will have prostate cancer diagnosed as a result of the PSA test¹, many of whom would have remained asymptomatic for life (i.e. are overdiagnosed).

**Overtreatment:**
- For every 1000 men tested,
  - 25 men will choose to undergo treatment (surgery or radiation) because of uncertainty about which cancers need to be treated, many of whom would do well without treatment (i.e. are overtreated)⁴.
  - 7–10 of these 25 men will develop persistent impotence and/or urinary incontinence, and some will develop persistent bowel problems, due to treatment⁴.
- For every 2000 men tested, 1 man will experience a serious cardiovascular event, such as myocardial infarction, due to treatment⁴.
Should I have prostate cancer screening?

Who is this information for?
This brief information sheet is designed to help you have an informed discussion with your GP. It is for:
- healthy men with no signs or symptoms (known as asymptomatic) and with no close blood relation with the disease
- aged 50–69 years
- who are considering a prostate specific antigen (PSA) blood test to screen for prostate cancer.
If you have a family history or any symptoms, such as difficulty passing urine, or other concerns about your prostate you should also speak to your GP.

What is prostate cancer?
Prostate cancer is a tumour (or growth of cell) that starts in the prostate gland. The prostate gland sits just below the bladder and is about the size of a golf ball. The prostate produces most of the fluid that makes up semen and nourishes the sperm.
There are different types of prostate cancer – most grow slowly and never cause harm, while others spread to other parts of the body and cause serious harm, and even death.

What increases my risk of prostate cancer?
Prostate cancer is more common as you get older. It is also more common if you have at least one close blood relative with prostate cancer (i.e., father, brother or son diagnosed under 65 years of age).

Where can I get information if I have a family history of prostate cancer?
Information has been developed for men with a family history of prostate cancer and is available on the NSW Health Department's Centre for Genetic Education website at www.genetics.edu.au/Genetic-conditions-support-groups/prostate-cancer-screening

What is prostate cancer screening?
Cancer screening is testing to detect a disease early before any signs or symptoms of disease, in order to treat the disease before it does any harm. The benefit of early testing and detection has to outweigh any potential harm.

There is significant debate about prostate cancer screening. This is because many prostate cancers that are detected are low risk (the slow growing type) and would never have caused harm to the man, but testing for and treating these cancers can cause harm.

Because of these issues, population-based screening is not recommended and there is no government organised national population prostate cancer screening program like there are for other cancers such as breast and bowel cancer.

What are my options?
You can choose to have the prostate cancer screening or decide not to have the test at this time. There is no right or wrong answer.
For men aged 50–69 (without a family history of prostate cancer) the benefit/harm debate for prostate screening using the PSA test is unclear and open to individual interpretation. Hence Australian guidelines support informed decision-making about prostate cancer screening based on personal circumstances. Since the decision to have prostate cancer screening is a personal one, it is up to the individual to request testing from their GP.

Figure 1 is designed to assist you in seeing the numbers of people affected by each option and help weigh up the benefits, harms and uncertainties of prostate cancer screening.

What are the tests for prostate cancer?
- Blood test for PSA. This test is controversial as a screening test because:
  - PSA levels may be elevated from causes other than prostate cancer
  - there is debate about what constitutes a "normal" and an "abnormal" PSA level when screening.
  - the test is often repeated if it is only mildly elevated
  - the PSA test does not discriminate between those cancers that will cause harm and those that will not (see "What is prostate cancer?" section above).
- Digital rectal examination, where the doctor inserts a finger into the anus to examine the prostate, is no longer recommended in addition to PSA testing.
A prostate biopsy may be recommended if there is an elevated PSA or a rapid rise in PSA. A biopsy is a procedure in which samples of prostatic tissue are removed. It is needed to confirm whether prostate cancer is present.

Extra 67 men with prostate cancer
87 men have biopsy and no prostate cancer (false positive)
28 men have side effects from biopsy requiring healthcare/hospitalisation
37 men have slow-growing cancers (over-diagnosis) and 25 men with choose to be treated (over-treatment)
7-10 men experience impotence and/or urinary incontinence or bowel problems
0.5 men have heart attack due to treatment
### Weighing up life gained against treatment side-effects

<table>
<thead>
<tr>
<th>Treatment related adverse effects</th>
<th>Additional months of life needed to compensate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild fatigue</td>
<td>3.25</td>
</tr>
<tr>
<td>Severe erectile dysfunction</td>
<td>4.00</td>
</tr>
<tr>
<td>Mild urinary leakage</td>
<td>4.22</td>
</tr>
<tr>
<td>Mild urinary blockage</td>
<td>4.91</td>
</tr>
<tr>
<td>Severe loss of libido</td>
<td>5.02</td>
</tr>
<tr>
<td>Mild bowel symptoms</td>
<td>6.22</td>
</tr>
<tr>
<td>Severe fatigue</td>
<td>13.30</td>
</tr>
<tr>
<td>Severe urinary blockage</td>
<td>21.96</td>
</tr>
<tr>
<td>Severe bowel symptoms</td>
<td>25.31</td>
</tr>
<tr>
<td>Severe urinary leakage</td>
<td>27.69</td>
</tr>
</tbody>
</table>

Source: King et al (2012)
**Take home messages**

<table>
<thead>
<tr>
<th>Offer men opportunity to discuss benefits and harms of PSA testing before making a decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harms of PSA testing may outweigh benefits particularly in men &gt;70</td>
</tr>
<tr>
<td>Men at average who decide to have regular testing should be offered PSA every 2 years from 50-69</td>
</tr>
<tr>
<td>Men with family history of prostate cancer who decide to be tested should be offered PSA every 2 years from 40/45 to 69 depending on risk of prostate cancer</td>
</tr>
<tr>
<td>DRE not recommended for asymptomatic men as part of PSA testing</td>
</tr>
</tbody>
</table>
Take home message
Discuss and inform first

Prostate exam
level: Rivals