Resolving the PSA testing controversy

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Introduction

• Guidelines aim to inform testing for the early diagnosis in men
  – Who are of an age when prostate cancer is likely to occur
  – Who do not have symptoms that suggest they have prostate cancer

• Multi-disciplinary Expert Advisory Panel which included
  – General practitioners (3)
  – Epidemiologists (2)
  – Urologists (5)
  – Medical oncologists (1)
  – Radiation oncologists (2)
  – Pathologists (2)
  – Psycho-oncologists (1)
  – Consumer representatives (3)
Introduction

- The Expert Advisory Panel agreed to proceed on the assumption that PSA testing is efficacious and reduces prostate cancer mortality to the extent estimated by the European Randomised Study of Screening for Prostate Cancer (ERSPC).
- The Expert Advisory Panel agreed on a series of clinical questions which were subsequently converted to PICO questions.
Clinical questions

Risk

• What risk factors can identify Australian men who are at high risk of prostate cancer or death from prostate cancer?
Clinical questions

Testing

• What variant of PSA testing is the best to use initially?
• What should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk and how should they be modified for men at high risk of prostate cancer?
• How best can DRE be used, if at all, in association with PSA testing?
Clinical questions

Testing

• What further tests for prostate cancer should be offered after an abnormal PSA test is obtained and before a prostate biopsy is offered?
• What age or health status criteria should be used to identify men who would be unlikely to live long enough to benefit from PSA testing and who, in consequence, would not be offered PSA testing?
• What methods of decision support for men about PSA testing increase men’s capacity to make an informed decision for or against testing?
Clinical questions

Investigation

• What constitutes an adequate prostate biopsy?
• If prostate cancer is not found in an adequate biopsy what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?
• What constitutes an adequate repeat prostate biopsy?
Clinical questions

Management

• What should be the criteria for choosing active surveillance or watchful waiting in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?

• What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?

• What is the best monitoring protocol for watchful waiting and what should be the criteria for intervention?
Guideline development process

• Guidelines developed in accordance with the procedures and requirements of Australia’s National Health and Medical Research Council
  – Process initiated by Prostate Cancer Foundation of Australia
  – Collaborative project between Prostate Cancer Foundation of Australia and Cancer Council Australia
  – Develop structured clinical question and PICO questions
  – Search for existing relevant guidelines and systematic reviews
  – Develop a systematic search strategy
  – Conduct systematic literature search according to protocol
  – Screen literature results against pre-defined inclusion and exclusion criteria
  – Critical appraisal and data extraction of each included article
  – Assess the body of evidence and formulate recommendations

• Literature review cut-off 1 March 2014
• Public consultation closes 16 January 2015
# Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention</th>
<th>Diagnosis</th>
<th>Prognosis</th>
<th>Aetiology</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A systematic review of level II studies &lt;br&gt;N = 1</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
</tr>
<tr>
<td>II</td>
<td>A randomised controlled trial &lt;br&gt;N = 45</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation</td>
<td>A prospective cohort study</td>
<td>A prospective cohort study &lt;br&gt;N = 2</td>
<td>A randomised controlled trial &lt;br&gt;N = 4</td>
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<tr>
<td>III-1</td>
<td>A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation</td>
<td>All or none</td>
<td>All or none</td>
<td>A pseudo-randomised controlled trial (i.e. alternate allocation or some other method) &lt;br&gt;N = 1</td>
</tr>
<tr>
<td>III-2</td>
<td>A comparative study with concurrent controls: &lt;br&gt;Non-randomised, experimental trial &lt;br&gt;Cohort study &lt;br&gt;Case-control study &lt;br&gt;Interrupted time series with a control group &lt;br&gt;N = 3</td>
<td>A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence &lt;br&gt;N = 35</td>
<td>Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial</td>
<td>A retrospective cohort study &lt;br&gt;N = 15</td>
<td>A comparative study with concurrent controls: &lt;br&gt;Non-randomised, experimental trial &lt;br&gt;Cohort study &lt;br&gt;Case-control study</td>
</tr>
<tr>
<td>III-3</td>
<td>A comparative study without concurrent controls: &lt;br&gt;Historical control study &lt;br&gt;Two or more single arm study &lt;br&gt;Interrupted time series without a parallel control group</td>
<td>Diagnostic case-control study</td>
<td>A retrospective cohort study</td>
<td>A case-control study</td>
<td>A comparative study without concurrent controls: &lt;br&gt;Historical control study &lt;br&gt;Two or more single arm study</td>
</tr>
<tr>
<td>IV</td>
<td>Case series with either post-test or pre-test/post-test outcomes</td>
<td>Study of diagnostic yield (no reference standard)</td>
<td>Case series, or cohort study of patients at different stages of disease</td>
<td>A cross-sectional study</td>
<td>Case series</td>
</tr>
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</table>
Professor Bruce Armstrong AM
PSA testing – Key clinical question

What should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk and how should they be modified for men at high risk of prostate cancer?
Evidence from six randomised controlled trials

Does PSA testing in asymptomatic men reduce their risk of dying from prostate cancer?

All six RCTs examined the effect of PSA testing on death from prostate cancer, but the findings were inconsistent. Of the two largest and most recent trials, one found that PSA testing led to a small but significant reduction in death from prostate cancer; the other found that PSA testing did not reduce death from prostate cancer. Thus, the present evidence is inconsistent as to whether PSA testing affects the risk of dying from prostate cancer.

NHMRC 2014
The two largest and most recent trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Started</th>
<th>Follow-up</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERSPC</td>
<td>182,160</td>
<td>1991</td>
<td>13 years</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.69-0.91)</td>
</tr>
<tr>
<td>PLCO</td>
<td>76,693</td>
<td>1993</td>
<td>10-13 y</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.87-1.36)</td>
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</table>

We chose to use the ERSPC results

- **PLCO**
  - 45% of men randomised had a PSA test in the 3 years before study entry
  - 52% of control group had PSA test in period of last PSA test in intervention group
  - 40% of intervention group men who had a positive PSA had biopsy within 12 months
We chose to use the ERSPC results

• ERSPC

  – 31% of control group had one or more PSA tests during the trial
  – ~90% of intervention group men who had a positive PSA were biopsied
  – Consistency of results across the 7 component centres: RR 0.56 to 0.89 with one exception
  – Evolution of difference in mortality between intervention and control groups exactly as expected from an efficacious test
ERSPC - Cumulative prostate cancer mortality to 13 years of follow-up

Schroder et al. Lancet – Published online 7th August 2014.
PSA testing – Protocol

Evidence-based guideline
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 ng/mL.

Grade C
PSA testing – Age at starting

Consensus-based recommendation
For men informed of the benefits and harms of testing 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 >95th percentile for age;
– Reconfirm offer of testing every 2 years if PSA $<95^{\text{th}}$ percentile and $>75^{\text{th}}$ percentile;
– Advise no further testing until age 50 if the initial PSA is $<75^{\text{th}}$ percentile for age
Why 45 years?
Prostate cancer mortality by age
Australia 1991-95
Cumulative risk % of prostate cancer death by age, PSA level and time

Why >95\textsuperscript{th} percentile?
Modelled outcomes of PSA testing

• 47 screening protocols modelled (age at start and stop, interval between tests, criterion for biopsy) in MISCAN and FHCRC models

• Outcome variables extracted:
  – Probability % of ≥1 false positive
  – Probability % of an over-diagnosis
  – Probability % that prostate cancer death is prevented
  – Mean months of life gained per man tested
  – Number needed to diagnose to prevent one death
  – Mean months of life gained per man diagnosed
PSA testing – High risk men

Consensus-based recommendation
For men who have risk factors that place them at a two and a half- to three-fold or higher risk of prostate cancer than average:

– offer testing every two years from 45–69 years of age rather than 50–69 years of age
– offer further investigation if PSA is >95th percentile for age;
– Reconfirm offer of testing every 2 years if PSA <95th percentile and >75th percentile;
– Advise no further testing until age 50 if the initial PSA is <75th percentile for age
Increase in prostate cancer mortality/100,000/year over next 10 years of age (Australia 1991-95)

<table>
<thead>
<tr>
<th>Relative risk of prostate cancer</th>
<th>Age 40</th>
<th>Age 45</th>
<th>Age 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 (av. risk)</td>
<td>2.34</td>
<td>7.98</td>
<td>22.69</td>
</tr>
<tr>
<td>2.0</td>
<td>4.67</td>
<td>15.96</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>5.84</td>
<td>19.95</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>7.01</td>
<td>23.94</td>
<td></td>
</tr>
<tr>
<td>3.5</td>
<td>8.18</td>
<td>27.93</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>9.34</td>
<td>31.92</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>11.68</td>
<td>39.91</td>
<td></td>
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</tbody>
</table>
PSA testing – Life expectancy

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

Grade C
Digital rectal examination

Evidence-based recommendation

For asymptomatic men interested in undergoing testing for early diagnosis of prostate cancer, digital rectal examination (DRE) is not recommended as a routine test in the primary care setting.

Grade C
Trade-off of additional true and false positive tests when DRE is added to PSA testing

Thompson et al. J Urol 2007; 177: 1745-52
Evidence-based decisional support

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

Grade C
Professor
Mark Frydenberg
Clinical Importance

• Previously multiple different recommendations from different sources
  – Mixed messages to men, GPs and specialists,
  – Confusion
  – Strong need for guidance for men and GPs from all the varied groups/stake-holders within Australia

• Why confusion?
  – Screening vs testing
  – Evidence based vs mixed evidence and consensus based
What to do if PSA is borderline or abnormal?

If borderline – PSA 2-3ng/mL – in high risk men
• Repeat PSA with free/total ratio, consider referral and biopsy if ratio < 25%

If abnormal
• Repeat with free/total ratio in men aged 50-69 years whose PSA is between 3 and 5.5 ng/ml, consider referral and biopsy if ratio < 25%
• If men decline biopsy, a warning should be provided that there is a small chance of missing a significant cancer and PSA with free/total ratio should be measured again within 6 months
Biopsy

• Take 21-24 cores in initial biopsy
  – Improves accuracy of diagnosis with regards to tumour volume and grade
  – Trans-rectal and trans-perineal biopsy approaches both acceptable
  – Take into account surgeons experience, risk of sepsis, access to facilities
Biopsy

• If initial normal biopsy
  - Men must continue to be followed up
  - Monitor more closely if abnormal DRE, or if biopsy identified atypical small acinar proliferation or high grade prostate intra-epithelial neoplasia
  - If repeat biopsy is considered, offer a multi-parametric MRI prostate, done in specialized centres, to determine if biopsy is required and to assist in localization of biopsy
  - MRI should not be ordered by GPs and only by specialists in order to aid with biopsy
  - MRI should only be used in men who have had previous biopsy
  - If MRI is normal, recommend further biopsy is not required but warn there may be 10-15% chance of missing a significant cancer and follow up is recommended
Active surveillance (AS)

- Offer active surveillance if low risk features exist
  - PSA < 20 ng/ml, Clinical stage T1-2, Gleason 6 cancers
  - Take into account other factors – core numbers, core length, PSA doubling time, PSA density
  - Risk of death over 10 years would be no greater than if they were to choose immediate treatment
- Consider active surveillance
  - In men with PSA < 10 ng/ml, Clinical stage T1-2a cancer and Gleason ≤ 3+4 (≤10%) =7, including in younger men < 60 years of age
  - In men with PSA 10-20 ng/ml, Clinical stage T2a/b consider definitive treatment or repeat biopsy if AS strongly preferred by patient
Active surveillance - Monitoring

- Monitor with PSA each 3 months, and DRE each 6 months
- Monitor with re-classification biopsy within 6-12 months of starting AS program
- If not re-classified, offer repeat biopsies (± MP MRI) each 2-3 years or earlier as needed to investigate clinical progression
- Offer treatment if disease progression detected at repeat biopsy or if patient prefers to proceed to intervention
Watchful waiting (WW)

• Offer WW if
  – Patient is unlikely to live for another 7 years
  – Chooses not to accept definitive therapy when offered to them
  – Warn that the risk of developing more advanced prostate cancer and dying greater than if chose immediate definitive treatment.
  – WW unlikely to diminish well being and quality of life in medium to long term
Watchful waiting - Monitoring

• Should be monitored by specialist or GP each 3 months with PSA
• If no symptoms and minimal change in PSA continue 6 monthly monitoring
• If symptomatic local disease progression, symptomatic or proven metastasis, PSA doubling time < 3 months refer back to treating specialist team
• Consider use of androgen deprivation therapy at that time
Questions
Thank You