PSA testing in New Zealand general practice

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On behalf of the Midland Prostate Cancer Study Group

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Why screen?

- Will my patient be more likely to live longer and be healthier if they take part in a screening program for prostate cancer?
- Will my patient be less likely to die from prostate cancer if they take part in a screening program for prostate cancer?
Presentation

- Evidence about screening – Ross Lawrenson
- What we found in a sample of 31 practices in the Midland region – Charis Brown
- Patient perspective – Charis Brown
- Summary/Questions/Discussion

Testing vs screening

- NZ GPs do 250,000 PSA tests per year
- 80%+ of these are in asymptomatic men and can be considered opportunistic testing
- The select Committee report called it “disorganised screening”
- Most NZ GPs think screening is worthwhile (while UK GPs for instance do very little screening)
- GPs get conflicting advice from Ministry, Urology association/local specialists, path labs
Statements on screening

- “many men are harmed as a result of prostate cancer screening and few if any benefit” – US Preventative Task Force 2011
- “Men in the 50 – 70 age group with at least 10 years life expectancy should be able to be screened” Urological Society of Australia and New Zealand
- “Men interested in their prostate health could have a single PSA test and DRE performed at or beyond age 40”

Screening Criteria

- Suitable candidate for screening
- There is a suitable test
- There is an effective and accessible treatment or intervention for the condition
- There is high quality evidence, ideally from randomised controlled trials, that a screening programme is effective in reducing morbidity or mortality
- The potential benefit should outweigh the potential harm
- The health care system will be capable of supporting all necessary elements of the screening pathway
- There is consideration of social and ethical issues
- There is consideration of cost-benefit
Suitable candidate for screening

- Important cause of mortality in men – 590 deaths per year in NZ and 2900 new cases pa

Deaths from prostate cancer in NZ 1948 to 2007
Number of deaths from prostate cancer by age group in New Zealand 2007

Age standardised incidence of prostate cancer per 100,000 men in NZ 1948 to 2007
Suitable candidate for screening

- Important cause of mortality in men – 590 deaths per year in NZ
- Long lead time

Natural history

- Most localised prostate cancer has an indolent course during the first 10 to 15 years.
- Johansson (1997) showed that in a population-based cohort of men with prostate cancer after 15 years of follow up, 80% of men who had initially presented with localised disease were alive
- Survival was unaffected by whether or not they had received treatment.
- Further follow up at 15 to 20 years revealed a substantial decrease in cumulative progression-free survival.
There is a suitable test

- Prostate-specific antigen (PSA) identifies a significant proportion of men who have no evidence of cancer as well as some men who have evidence of cancer but in whom it is unlikely to become symptomatic and thus have no increased risk (false positives).
- Cut off point of 4 ng/mL will miss some men with cancer including a small number who may have undifferentiated tumours with a high Gleason score (false negatives).
- Lowering the cut off point to 3 ng/mL or lower as was done in the European Randomised Screening in Prostate Cancer study increased the sensitivity but also increased the number of false positives.

**Johannson JAMA 1997**
642 patients with prostate cancer diagnosed between 1977 and 1984 at a mean age of 72
There is a suitable test

- Cut off point in older men?
- PSA velocity?
- New variations e.g. Free PSA, PHI

There is an effective and accessible treatment or intervention for the condition

- Options for treatment include:
  - Radical prostatectomy,
  - Radiotherapy (focussed beam, or brachytherapy),
  - Active surveillance.
- We have evidence from an RCT of radical prostatectomy versus watchful waiting - fewer men in the radical prostatectomy group died of prostate cancer (30 vs. 50, P=0.01) (Bill-Axelson et al 2005).
- PIVOT showed no benefit from prostatectomy
- There is little convincing evidence that brachytherapy or focussed beam radiotherapy have different survival outcomes than prostatectomy.

PIVOT study

- Trial of active surveillance vs prostatectomy in localised cancer
Active surveillance

- Monitor men with localised low grade disease with PSA and repeat biopsies
- Intervene if biopsy show increasing Gleason score or increasing number of cores+
- Usually localised disease, PSA less than 10 and Gleason score less than 7 is considered suitable for AS
What about complications?

- Main controversy in treating prostate cancer is that need to balance improved life expectancy versus complications of treatment
Complications

Table 2. Patient-Reported Urinary, Erectile, and Bowel Dysfunction at 2 Years, According to Study Group.©

<table>
<thead>
<tr>
<th>Dysfunction</th>
<th>Radical Prostatectomy</th>
<th>Observation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>49/287 (17.1)</td>
<td>18/284 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>231/285 (81.1)</td>
<td>124/281 (44.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bowel dysfunction</td>
<td>35/286 (12.2)</td>
<td>32/282 (11.3)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Harm of treatment ("Let sleeping dogs lie")

Table 3: Prevalence of urinary incontinence, bowel problems, and sexual impotence, three years after treatment and in untreated controls (percentages). EBRT, external beam radiation therapy; ADT, androgen deprivation therapy.

<table>
<thead>
<tr>
<th>Urinary incontinence</th>
<th>Active surveillance</th>
<th>RP total</th>
<th>Nerve sparing RP</th>
<th>Nerve sparing BP</th>
<th>EBRT</th>
<th>ADT</th>
<th>Combined EBRT/ADT</th>
<th>Low dose brachytherapy</th>
<th>High dose brachytherapy</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6.0</td>
<td>1.1</td>
<td>0.6</td>
<td>1.4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>three years</td>
<td>0.1</td>
<td>0.4</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe bowel problems</td>
<td>13.5</td>
<td>1.1</td>
<td>3.6</td>
<td>5.3</td>
<td>10.6</td>
<td>10.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>2.0</td>
</tr>
<tr>
<td>three years</td>
<td>6.2</td>
<td>0.6</td>
<td>0.1</td>
<td>2.7</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Impotence</td>
<td>27.3</td>
<td>21.5</td>
<td>15.6</td>
<td>27.6</td>
<td>30.2</td>
<td>42.1</td>
<td>19.1</td>
<td>19.0</td>
<td>25.3</td>
<td>22.3</td>
</tr>
</tbody>
</table>
So is there evidence from RCTs that screening is beneficial?

- ERSPC
- PLCO
- Goteborg

**European Randomized Study of Screening for Prostate Cancer (ERSPC)**
- Included 182,000 men recruited over 10 years from 7 different European countries
- Men aged 55 to 75 years
- Screened men every 4 years
- Considered positive if test greater than 2.4 ng/ml
ERSPC

- Early evidence from ERSPC published in March 2009. The trial **analysed** men from ages 55 to 69 years
- The European trial reported a significant absolute risk difference between the screening and control groups of **0.71 prostate cancer** deaths per 1000 men.
- 1410 men would have to be screened 1.7 times over 9 years (number needed to screen), and 48 men would need to be treated (number needed to treat) to prevent one prostate cancer death.
- There was no benefit in all cause mortality

### Table 2. Death from Prostate Cancer, According to the Age at Randomization.

<table>
<thead>
<tr>
<th>Age at Randomization</th>
<th>Screening Group</th>
<th>Control Group</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>Person-Yr (Death Rate per 1000 Person-Yr)</td>
<td>No. of Deaths</td>
</tr>
<tr>
<td>All subjects</td>
<td>261</td>
<td>737,397 (0.35)</td>
<td>363</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54 yr</td>
<td>6</td>
<td>55,241 (0.11)</td>
<td>4</td>
</tr>
<tr>
<td>55–59 yr</td>
<td>60</td>
<td>316,389 (0.19)</td>
<td>102</td>
</tr>
<tr>
<td>60–64 yr</td>
<td>76</td>
<td>191,542 (0.40)</td>
<td>95</td>
</tr>
<tr>
<td>65–69 yr</td>
<td>78</td>
<td>135,470 (0.58)</td>
<td>125</td>
</tr>
<tr>
<td>70–74 yr</td>
<td>74</td>
<td>38,755 (1.06)</td>
<td>33</td>
</tr>
</tbody>
</table>
PLCO

- 180,000 men and women recruited in US for a study of prostate, lung, colorectal and ovarian cancer
- 76,693 men randomised
- Aged 55 to 75 years
- Screened men every year
- 2820 cancers in screening group, 2323 in control
- 50 deaths from PC in screening group and 44 in control group

PLCO

- Smaller sample size
- Older patient group
- Significant contamination in control group
Goteborg

- Included 20000 men recruited over 10 years from Sweden (part of ERSPC)
- Men aged 50-64 years
- Screened men every 2 years
- Considered positive if test greater than 2.9 ng/ml (reduced to 2.4 later in study)

Goteborg study (2010)

- In the screening group, the participation rate in at least one screening round was 76% (n=7578) and a total of 29315 PSA tests were performed.
- A total of 4693 positive PSA results were recorded.
- 33% of the participants (n=2469) received at least one positive result and 93% of these (n=2298) had a biopsy performed.
Goteborg study (2010)

- After 14 years of follow-up, within a core age group of 50 to 64 years, 44 and 78 prostate cancer deaths were observed in the screening group and control groups respectively.
- The unadjusted rate ratio for death from prostate cancer in the screening group was 0.56 (95% CI, 0.39-0.82 p=0.002) i.e. A 44% reduction in prostate specific cancer deaths.
- The incidence of prostate cancer was almost 60% greater in the screened group (see table).
- The all cause mortality in the two groups was 1982 in the control group and 1981 in the screened group.

<table>
<thead>
<tr>
<th>Goteborg study</th>
<th>Control Group</th>
<th>Screened Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with prostate cancer</td>
<td>718</td>
<td>1138</td>
</tr>
<tr>
<td>Number of prostate cancer deaths</td>
<td>78</td>
<td>44</td>
</tr>
<tr>
<td>Number with prostate cancer who died of unrelated causes</td>
<td>54</td>
<td>109</td>
</tr>
</tbody>
</table>
Trends?

- Death rate in New Zealand
- What about metastatic disease?

Age standardised death rates from prostate cancer in NZ 1948 to 2007
Conclusions

- Some evidence from RCTs that screening men aged 50-69 every 2-4 years with a cut off of 2.4ng/ml will reduce number of prostate cancer deaths after 9-14 years
- Screening asymptomatic men will lead to over diagnosis and potential harm – harm could be reduced if more use of active surveillance
- No evidence that screening men over aged 70 years reduces deaths from prostate cancer and certainly should not screen men over 75 years
- Uncertainty as to cut off points – lower levels lead to higher referral and biopsy rates
- When to re-screen if PSA is normal – ERSPC was 4 year interval and Goteborg was 2 years
Midlands Prostate Cancer Study

**Phase 1**: To examine the patterns of prostate-specific antigen (PSA) testing in primary care

**Phase 2**: To understand national prostate cancer statistics with focus on regional and ethnic differences

**Phase 3**: To follow the pathways and treatment options within the Midland region

**Phase 4**: To estimate the cost and complications of treatment, incl. the impact on men and their families

**Method**

- Clinic recruitment and consent to access labs data (pilot = 5 clinics; study 26 clinics)
- Access and clean laboratory data – men 40 years plus, currently registered in recruited clinic, PSA tested during 01/01/2010 to 31/12/2010
- Medtech search on each practice computer system - reason for PSA, follow-up care, referral, biopsy and any diagnosis
- Men with elevated PSA levels in 2010 were sent a patient questionnaire
Practice Characteristics

- 19 Waikato, 8 Bay of Plenty, 4 Lakes DHBs
- The population size of the communities were well spread, from: <10,000: 11; 10,000-30,000: 9; >30,000: 12
- 13 Urban providers; 18 rural (incl. 11 rural allowance)
- 9 Maori providers (4180)
- The distance from GP to cancer centre varied: 0-9km: 7; 10-99km: 9; 100+km: 15

Practice baseline: Men 40yrs plus

- 31 clinics
- 35,964 men
- 14% M, 84% n-M
Frequency of Men PSA tested

- Total: 9,348 men tested (26.0%)
  - Maori: 26.8% n-M
  - non-Maori: 12.9% M

Frequency of elevated PSA

- Total: 1,081 men had elevated PSA (11.6%)
  - M more likely to have elevated result
Clinic Testing

Screened Men (proportion of tests)

85% of men tested were screened 7946/9348

Total

60-69y

70-79y

80-89y

90-99y

40-49y
Elevated PSA in screened men

Only 2% of screened men had an elevated PSA (171/7946)

Summary of men tested

<table>
<thead>
<tr>
<th></th>
<th>non-Maori</th>
<th>% non-Maori</th>
<th>Maori</th>
<th>% Maori</th>
<th>Unknown ethnicity</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PSA tests</td>
<td>8067</td>
<td>27.6%</td>
<td>651</td>
<td>12.8%</td>
<td>630</td>
<td>9348</td>
</tr>
<tr>
<td>Total elevated</td>
<td>975</td>
<td>11.5%</td>
<td>92</td>
<td>12.9%</td>
<td>14</td>
<td>1081</td>
</tr>
<tr>
<td>Total men screened</td>
<td>6795</td>
<td>84.20%</td>
<td>559</td>
<td>85.90%</td>
<td>592</td>
<td>7946</td>
</tr>
<tr>
<td>(from all PSA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screened elevated</td>
<td>145</td>
<td>2.10%</td>
<td>24</td>
<td>4.30%</td>
<td>2</td>
<td>171</td>
</tr>
<tr>
<td>(elevated out of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>screened)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total men non-</td>
<td>1272</td>
<td>15.80%</td>
<td>92</td>
<td>14.10%</td>
<td>38</td>
<td>1402</td>
</tr>
<tr>
<td>screened</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-screened</td>
<td>830</td>
<td>65.30%</td>
<td>68</td>
<td>73.90%</td>
<td>12</td>
<td>910</td>
</tr>
<tr>
<td>elevated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
After a raised result
468 Referrals made from 1081 Men with Elevated PSA (by screening or non-screening)

Median PSA referral level

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal value range</th>
<th>Screened men</th>
<th>Non-Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49y</td>
<td>0 - 2.5</td>
<td>3.50</td>
<td>3.30</td>
</tr>
<tr>
<td>50-59y</td>
<td>0 - 3.5</td>
<td>6.13</td>
<td>5.35</td>
</tr>
<tr>
<td>60-69y</td>
<td>0 - 4.5</td>
<td>6.50</td>
<td>8.60</td>
</tr>
<tr>
<td>70-79y</td>
<td>0 - 6.5</td>
<td>10.70</td>
<td>9.84</td>
</tr>
<tr>
<td>&gt;80y</td>
<td>0 - 7.0</td>
<td>38.46</td>
<td>14.30</td>
</tr>
</tbody>
</table>
### After a raised result

#### 303 Referred Men Biopsied
(by screening or non-screening)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Screened</th>
<th>Non-screened</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>80+</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>70-79</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>50-59</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>40-49</td>
<td></td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

#### 159 Positive Biopsy Results
(by screening or non-screening)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Screened</th>
<th>Non-screened</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>80+</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>70-79</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>50-59</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>40-49</td>
<td></td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>
Prostate Cancer through Screening

<table>
<thead>
<tr>
<th>Mean age</th>
<th>64.5</th>
<th>SD: 7.54</th>
<th>Min: 43</th>
<th>Max: 76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>23 NZ European</td>
<td>4 Maori (13.8%)</td>
<td>1 Other European</td>
<td>1 Cook Islands Maori</td>
</tr>
<tr>
<td>Median (mean) PSA</td>
<td>7.82 (17.79)</td>
<td>SD: 37.18</td>
<td>Min: 1.72</td>
<td>Max: 203.25</td>
</tr>
<tr>
<td>No. of cores</td>
<td>1-3: 12 (41.4%)</td>
<td>4-6: 9 (31.0%)</td>
<td>7+: 7 (24.1%)</td>
<td>1 unknown</td>
</tr>
<tr>
<td>Gleason score</td>
<td>6: 15 (51.7%)</td>
<td>7: 9 (31.0%)</td>
<td>8: 1 (3.4%)</td>
<td>9: 4 (13.8%)</td>
</tr>
<tr>
<td>Clinical stage (3 no info)</td>
<td>T1c: 9 (31.0%)</td>
<td>T2: 12 (41.4%)</td>
<td>T3: 4 (13.8%)</td>
<td>T4: 1 (3.4%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>RP: 13 (44.8%)</td>
<td>RT: 5 (17.2%)</td>
<td>AS: 7+4 (with no direct info) (24.1% or 37.9%)</td>
<td></td>
</tr>
</tbody>
</table>

What do GPs say?

Method: Questionnaire sent to GPs in the pilot 5 practices, 18/26 surveys returned (69%)

- 17/18 admitted to screening (selective and/or opportunistic)
- 61% agreed PSA testing reduced mortality rates
- 55% believed benefits of testing outweighed harm
- 44% agreed that all men over 40 should be tested
What do GPs say?

- 72% did DRE + PSA test
- 39% felt they needed more knowledge
- 56% felt it was difficult to give balanced view
- 61% said patients elected to be tested anyway post consultation

What do GPs say?  18/26 surveys returned (69%)

- Questionnaire sent to GPs in the 5 practices
  - 17/18 admitted to screening (selective and/or opportunistic)
  - 61% agreed reduced mortality rates
  - 55% believed benefits outweighed harm
  - 44% agreed PSA test all men over 40
  - 72% did DRE + PSA test
  - 39% felt need more knowledge
  - 56% felt difficult to give balanced view
  - 61% said patients elected to be tested anyway
Conclusions

- PSA testing is common place
- Majority is screening
- Varies considerably by practice
- More likely to find elevated result in Maori from screening
- Overall a positive test in screened (asymptomatic) group was 2% - likely to be due to repeat testing
- Nearly 20% of men screened were 70 years or older
- Men with a positive test, 43% were referred
- Once referred, 65% biopsied
- 51% of men biopsied had cancer

Participant Point of View: Phases 1&4

**Phase 1:** To examine the patterns of prostate-specific antigen (PSA) testing in primary care

**Phase 2:** To understand national prostate cancer statistics with focus on regional and ethnic differences

**Phase 3:** To follow the pathways and treatment options within the Midland region

**Phase 4:** To estimate the cost and complications of treatment, incl. the impact on men and their families
Phase One Patient Surveys

Method: Patients from all GP practices with a first raised PSA in 2010 were sent a patient survey.

Results:
- 394 men from 31 clinics.
- 42 ineligible men removed.
- 225 eligible responses received (90% European).
- Response rate: 64%

Findings

Patients had varied knowledge of their PSA test:
- Not all patients knew how many PSA tests they had.
- Majority of men were prompted by their GP to have the test.
- 30% of men felt they had requested the test from their GP. Family history, changes in urinary patterns, and a growing awareness of PSA testing and PCa was frequently mentioned.
Findings

Symptoms:
• The bulk of men did not present to the GP with symptoms (58%).
• For those men that did have symptoms (42%) the majority of presenting symptoms were urinary frequency, and haematuria.
• 75% of men had a DRE at the time of the test.

Findings

Referrals:
• 58% of men were referred to a specialist.
• Most men who were referred went to see a specialist in private.
• The specialist was identified as having organised a biopsy by 67% of men.
• 26 men had a positive biopsy result.
Findings

Wait times:

<table>
<thead>
<tr>
<th>Wait time from GP to first specialist appointment</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 weeks</td>
<td>32</td>
</tr>
<tr>
<td>2-4 weeks</td>
<td>40</td>
</tr>
<tr>
<td>4-8 weeks</td>
<td>41</td>
</tr>
<tr>
<td>8-16 weeks</td>
<td>12</td>
</tr>
<tr>
<td>16-26 weeks</td>
<td>5</td>
</tr>
<tr>
<td>more than 26 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

Summary

- High rates of screening
- Mainly initiated by GPs
- Lower rates in Maori
- Conservative referral rates
- Screening considerable number of men aged over 70
- Uncertain what to do if PSA negative