Early Detection of Prostate Cancer:

How to do it ‘smart’

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If screening was a pill:

• You are a 60 year old male and are offered a pill which would
  • double your lifetime risk of prostate cancer diagnosis from 10% to 20%
  • decrease your lifetime risk of cancer death by 33% (from 3% to 2%)
• Would you take it?
US Preventive Services Task Force (USPSTF) summary on PSA screening 10/2011:

• “Small to no reduction in 10 year prostate cancer mortality”

• Harms related to false-positive results, including overdiagnosis and overtreatment

• “The Task Force recommends against PSA-based screening……a Grade D recommendation.”
<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial.</td>
<td>Offer/provide this service.</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.</td>
<td>Offer/provide this service.</td>
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<tr>
<td>C</td>
<td>The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.</td>
<td>Offer/provide this service only if other considerations support offering or providing the service in an individual patient.</td>
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<td>D</td>
<td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.</td>
<td>Discourage the use of this service.</td>
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<td>I</td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td>
<td>Read &quot;Clinical Considerations&quot; section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.</td>
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Urology responds to USPSTF

• Lacy AUA: "We are concerned that the task force's recommendations will ultimately do more harm than good …both in the US and around the world."

• “Until there is a better widespread test for this potentially devastating disease, the USPSTF -- by disparaging the test -- is doing a great disservice to the men worldwide who may benefit."

• Marberger EAU: “Mortality is reduced by PSA screening, but it has to be done in younger and fit patients who have a life expectancy for whom this slow growing cancer can really be a threat,”
2 options to USPSTF—Head in sand, or screen smarter
Prostate Cancer “Screening” Trials

- Norrköping
- Quebec Study (RCT) – 1998
- Swedish Study (RCT) – 2004
- Tyrol Study – Population comparison (+ screen effect)
- PLCO
- ERSP
- Göteborg
- ProtecT (UK) ongoing

Deviations / limitations
In statistical methods

Intent to treat, data and safety monitoring, scientific rigor, competent researchers
(Reported 2009, 2010)
ERSPC

Goteborg
NNS 293
NNT 12

PLCO All

Healthy men: NNS 723; NNT 5
PLCO: A problematic study

- Pre-randomization testing: 44% PLCO vs 3% Swedish trial
- Contamination: Powered for 38%
- 85% had at least 1 PSA by year 5 in the usual care arm, vs 24% in ERSPC (Rotterdam)
  - Pinsky Clin Trials 2010 7:303
- Nonattendance: 15% PLCO, 17.4% ERSPC
- Difference in PSA testing by randomized arm:
  - PLCO 85% vs 85% = 0 (NO DIFFERENCE)
  - ERSPC 82% vs 24%-58%
- Vickers JCO: Power of PLCO to find a difference = 12%
PSA screening and QALYs from ERSPC

- Gain up to 97.1 or loss up to 20.7 QALYs (big range)
- Depends on individual utilities
- Utilities: Captures the risk associated with a decision for treatment for that individual’s risk tolerance
- Wide limits support value of patient education and shared decision making
The USPSTF position on PSA screening—what it neglected to mention

- PLCO, a flawed study, still showed a significant reduction in Pca mortality in healthy men after 7 years, NNT=5 (JCO 2011:29:355-61)

- The Goteborg trial: 44% reduction in Pca mortality.
  - 40% of men were managed with surveillance—overtreatment can be addressed Lancet Oncol 2010:11:725

- Did not consider benefits of surveillance on NNT

- Adjusting ERSPC for non-compliance and contamination showed substantial improvement in NNS and NNT

- 40% reduction in Pca mortality in US since PSA introduced; modelling ascribes 50% of this to early detection

- High risk populations (ie, blacks) have not been adequately studied

- New molecular tests, imaging will help with decision making
Thoughts

• Screening doesn’t work for all cancers: Lung, neuroblastoma, and not all breast cancers
• Need to separate diagnosis from treatment; overtreatment clearly a problem
• But, need to remember that 30,500 men (US and Canada) died in 2012 of CaP
• We need to figure out who needs to be diagnosed and effectively treated.
PSA at age 60 and death or metastasis from prostate cancer: Vickers A et al BMJ 2010;341

- Blood from 1167 Swedish men age 60 taken in 1981
- No screening
- Likelihood of Pca met or death at 20 years
- If PSA < 1.0 at age 60, Met in 0.5%, death 0.2%
Predictive value of early PSA
Vickers, Ulmert, Sjoberg et al, BMJ 2013:348, 12023

- 21,277 men aged 33-50, 74% participation
- Low rates of PSA testing
- 1369 clinical pca, 241 metastases, 163 cancer deaths
- Age 45-49:
  - median PSA 0.7,
  - top quartile PSA 1.1
  - top decile 1.6.
- Probability of mets at 20-25 yrs in men with PSA < 1.1 ~ 0.2%.
PLCO Projections extrapolated to 200,000 cases of incident prostate cancer

- Two year screening interval:
  - Estimated national savings of $964 million (men age $\geq 55$ with localized PCa).
  - Estimated 0.6% missed clinically significant PCa cases.
  - Estimated 1% missed non-significant PCa cases.

- Five year screening interval:
  - Estimated national savings of $3.9$ billion (men age $\geq 55$ with localized PCa).
  - Estimated 1.2% missed clinically significant PCa cases.
  - Estimated 1.9% missed non-significant PCa cases.
Criticisms of USPSTF recommendation:

- Covered ALL asymptomatic US men regardless of age, race, or family history.
- Did not consider increased utilization of active surveillance (decreased NNT)
- Considered the ERSPC survival reduction “minor”
- No acknowledgement of benefits (metastasis reduction)
- Statement excessively focused on treatment complications
Conclusions

- A more rational policy is to screen based on risk and treat only those with significant PCa.
- The USPSTF findings should be viewed as an opportunity to do this.
‘Smart PSA screening’

- 1st test age ~ 45; if < 1, then repeat q 5 years
- Use only 2-3 tests between ages 55-65
- Best data: 98 screened and 5 cancers detected to prevent one pca death
- Screening above age 70 not recommended.
- Risk stratification for screening and for biopsy
- Role for additional blood/urine markers.
- Active surveillance for most low risk disease
- Emerging role for MRI to replace biopsy
Who to screen?

- Young, healthy, and/or high risk
- Benefit begins 6-7 years later (early)
- PSA and PSA kinetics more accurate pre BPH
- Longer life expectancy
- Greater likelihood of experiencing the benefit of early detection
- The test is better than we give it credit for!
## US Screening Recommendations 2012

**US Guidelines**

<table>
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<th>Organization</th>
<th>Recommendations</th>
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<tr>
<td>American Cancer Society (ACS)</td>
<td>1. Not in favor of routine screening&lt;br&gt;2. After informed discussion held for those who wish to be screened:&lt;br&gt;   - Screen all men with PSA, with or without DRE, at 50 years of age with &gt; 10 years life expectancy&lt;br&gt;   - Screen men at 45 years of age with high risk&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;   - Screen men at 40 years of age with highest risk&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;   - No screening in any man &gt; 75 years of age</td>
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<td>American College of Physicians (similar to the ACS)</td>
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<tr>
<td>National Comprehensive Cancer Network (NCCN)</td>
<td>1. Baseline DRE and PSA at 40 years of age&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;2. Repeat screening at 45 years of age if PSA &lt; 1.0 ng/mL&lt;br&gt;3. Annual screening at 50 years of age&lt;br&gt;4. Informed discussion with all patients</td>
</tr>
<tr>
<td>American Urological Association</td>
<td>1. Baseline DRE and PSA at 40 years of age&lt;br&gt;2. Screening stopped at age 75, but may be continued if the patient has a life expectancy of 10 years or more&lt;br&gt;3. Informed discussion with all patients</td>
</tr>
<tr>
<td>Organization</td>
<td>Recommendation</td>
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<td>European Association of Urology</td>
<td>1. Against national screening due to risk of over-treatment</td>
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<tr>
<td>U.K. National Health Services</td>
<td>2. Men should be evaluated on case by case basis and discuss all risks and</td>
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<tr>
<td>New Zealand National Health Committee</td>
<td>benefits with their physician</td>
</tr>
<tr>
<td>Japanese Urological Association</td>
<td>1. Baseline PSA, with or without DRE, at 40 years of age</td>
</tr>
<tr>
<td></td>
<td>2. Annual PSA at 50 years of age</td>
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<tr>
<td></td>
<td>3. No upper age limit cut-off for PSA testing</td>
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Google ‘Prostate cancer risk calculator’

Prostate Risk Calculator

The nomogram-based Sunnybrook Prostate Cancer Risk Calculator incorporates all known risk factors and tumour markers for prostate cancer and calculates an individual’s risk for prostate cancer.

To use this calculator, you need to know the following factors about yourself, or your patient:

1. Current age
2. Ethnic background
3. Family history of any relatives diagnosed with prostate cancer
4. The presence of urinary symptoms (measured by the International Prostate Symptom Score index)
5. Total PSA value
6. Free total PSA ratio value
7. Digital rectal exam (DRE) results of prostate (done by a physician)

Using these parameters, the Sunnybrook Prostate Cancer Risk Calculator has been shown to be more accurate than the conventional method of just using PSA and DRE results alone. It has also been validated from other patient populations and performs better than the U.S.-based prostate cancer risk calculator.

Results

Age: 65
IPSS (Urinary voiding Symptom score): 12
PSA: 5
FTPSA (Free:total PSA ratio): .16
Ethnic Background: Asian
Family history of prostate cancer: Yes
Abnormal DRE (by Doctor): No

![Prostate Risk of Cancer Chart]
Biomarker candidates: Many, but few selected

- PSA
- ProPSA/PHI
- CTC
- hK2
- Chromogranin
- NSE
- TGFbeta
- PSMA
- AMACR
- EPCA
- hK11
- Leptin
- MIF
- VEGF
- ZAG

Prostatic secretion
In Urine
After DRE

SERUM

BIOPSIES

SEMINAL PLASMA

PCA3
Gene Fusion
AMACR
LOH
Sarcosine
miRNA

...
PSA = 7.2, single core positive for Gleason 6
• Negative predictive value for ‘clinically significant’ PCa 95-98%
• Perhaps MRI with selective targeted biopsies an alternative to TRUS biopsy in men with elevated PSA
MRI for predicting upgrading in men on surveillance

- 388 men with favorable risk prostate cancer at MSKCC
- MRI prior to confirmatory biopsy
- Upgrading in 20%
- MRI score ≤2 had NPV 0.96-1.0 for upgrading
- MRI score of 5 had sensitivity for upgrading of 0.93
If screening was a pill:

- You are a 60 year old male and are offered a pill which would
  - double your lifetime risk of prostate cancer diagnosis from 10% to 20%
  - decrease your lifetime risk of cancer death by 20% from 3% to 2.4%

- Would you take it?
Prostate Cancer Screening: Benefits

- Earlier diagnosis
- 70% reduction in metastatic disease at diagnosis
- Cancer more localized and curable at diagnosis
- Likely 40-50% reduction in Pca mortality
Prostate Cancer Screening: Risks and Limitations

- Complications, QOL, and costs of treatment
- Lead time and length time bias
- PSAdynia
- Many require screening and treatment for each death avoided
TO-DO LIST

- Prevention
- Screen smarter
- Active surveillance
Conclusions

• Selective prostate cancer screening strategies applied to healthy men will enhance the benefit of prostate cancer screening

• Screen only healthy men aged 40-70

• Less frequent PSA (every 2-4 years) if PSA low

• Use age adjusted norms, follow borderline PSAs

• Consider alternatives to biopsy
Implications for Patient Care

• The real problem is not PSA (yes or no); rather
• The balance of quantity vs quality of life different for each patient
• Informed decision making (good patient brochure essential)
• Appreciate the heterogeneity of prostate cancer
• Reduce overtreatment: consider active surveillance for favorable risk cancer