PSA Screening: Science, Politics and Uncertainty

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The Science: Level I Evidence on Survival
Objective: To evaluate effect of annual PSA testing and DRE on prostate-cancer mortality.

Design: Randomized, Multicenter, 1993-2001

Methods:

• 76,693 US men, 50-74yrs randomly assigned to annual PSA screening (6yrs) and DRE (4yrs) or control group that did not receive such screening.

• Exclusion: PLCO cancer, >1 PSA in previous 3yrs.

• Further evaluation: PSA >4ng/mL or suspicious DRE

• Primary Outcome: Death from Prostate Cancer

• Intent-to-screen analysis

Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up

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.
The PLCO Trial
Not a comparison of Screening vs no Screening

Mean number of routine PSA tests
• 2.7 in control arm
• 5.0 in screening arm

Percent with at least one test:
• 74% in control arm
• 95% in screening arm

Numbers of cancers detected
• 1984 in control arm
• 1611 in concurrent population

► An excess of deaths on the screened arm is not unlikely – **15-28% chance**
► The power of the trial to detect a difference in mortality even if screening is beneficial is very low (less than 25%)
“When both groups were surveyed with the HSQ, men in the control group reported having had more cumulative PSA testing then men in the intervention group.”

Objective: To evaluate effect of PSA screening on prostate-cancer mortality.

Design: Randomized, Multicenter, 1991-2003

Methods:

- 182,000 men, 50-74yrs randomly assigned to PSA screening (avg q4yrs) or control group that did not receive such screening.
- 7 different European centers
- PSA cutoff: 3ng/mL* as indication for biopsy
- Primary Outcome: Death from Prostate Cancer
- Intent-to-screen analysis
- Number needed to invite (NNI), Number needed to detect (NND)

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

Figure 2: Nelson-Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)

• Total PCa deaths 299/72,891 in screen and 462/89,352 in control.
• Absolute mortality difference 1.28/1000 men randomized.
• Rate ratio for PC-specific mortality by years of f/u
  – 9 yrs: 0.85 (0.70-1.03)
  – 11 yrs: 0.78 (0.66-0.91)
  – 13 yrs: 0.79 (0.69-0.91)
• 781 men need to be invited and 27 additional cases of cancer detected to prevent one death.

Lives Saved By Screening: Trial versus Population?

**Short-term, trial (ERSPC)**

Prostate cancer deaths per 1,000 men invited in core age group after 11 years:

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.17</td>
</tr>
<tr>
<td>Screening</td>
<td>4.10</td>
</tr>
<tr>
<td>Absolute Difference</td>
<td>1.07</td>
</tr>
</tbody>
</table>

**Long-term, population (SEER)**

Prostate cancer deaths per 1,000 men invited starting at age 40 or 50 over lifetime:

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
</tr>
<tr>
<td>Screening</td>
<td>24</td>
</tr>
<tr>
<td>Absolute Difference</td>
<td>6</td>
</tr>
</tbody>
</table>
Short Term versus Long Term NND

What Is the True Number Needed to Screen and Treat to Save a Life With Prostate-Specific Antigen Testing?
Stacy Loeb, Edward F. Vonesh, E. Jeffrey Metter, H. Ballentine Carter, Peter H. Gann, and William J. Catalona

Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates
Roman Gulati, Angela B. Mariotto, Shu Chen, John L. Gore, Ruth Etzioni

Quality-of-Life Effects of Prostate-Specific Antigen Screening
Eveline A.M. Heijnsdijk, Ph.D., Elisabeth M. Wever, M.Sc., Anssi Auvinen, M.D., Jonas Hugosson, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Arnauld Villers, M.D., Alvaro Páez, M.D., Sue M. Moss, Ph.D., Marco Zappa, M.D., Teuvo L.J. Tammela, M.D., Tuukka Mäkinen, M.D., Sigrid Carlsson, M.D., Ida J. Korfage, Ph.D., Marie-Louise Essink-Bot, Ph.D., Suzie J. Otto, Ph.D., Gerrit Draisma, Ph.D., Chris H. Bangma, M.D., Monique J. Roobol, Ph.D., Fritz H. Schröder, M.D., and Harry J. de Koning, M.D.
Summarizing the Science

• Level I evidence is somewhat equivocal but favors a benefit in men above 50-55 through 70
  – PLCO has serious issues around contamination in the control arm, affecting the validity of the study
  – ERSPC is positive, but not overwhelmingly so
    • Goteborg site in ERSPC is strongly positive
    • Rotterdam site is weakly positive
  – Level II evidence and lower favors screening

GIVEN THESE OBSERVATIONS, WHY IS THERE ARE DEBATE?
PSA screening in the era of rising healthcare costs

THE POLITICS OF SCREENING
History of the US Preventive Services Task Force

• Government appointed expert panel formed in 1984 by the Office of Disease Prevention and Health Promotion within HHS

• Tasked to develop recommendations for primary care clinicians on the appropriate content of periodic health examinations
  – Composed of primary care doctors

• Reconstituted in 1990 and currently under the auspices of AHRQ (No final approval from AHRQ required)
  – 16 volunteer members: preventive medicine and primary care (internal medicine, family medicine, pediatrics, behavioral health, obstetrics/gynecology and nursing)
Why USPSTF matters now:
Thanks Obamacare

• Any preventive service that receives a “A” or “B” grade from USPSTF must be covered by Medicare with no co-payment from the beneficiary

• “Cost-sharing” is explicitly allowed for services that receive a “C”, “D” or “I” grade

• The language, as written, opens the door for private payors and Medicare to deny coverage for services with a “C”, “D” or “I” grade on a case by case basis.
USPSTF and PCa screening: Grade D

- The reduction in prostate cancer mortality 10 to 14 years after PSA-based screening is, at most, very small, even for men in the optimal age range of 55 to 69 years.

- The harms of screening include pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, psychological harm of false-positive test results, and overdiagnosis.

- Harms of treatment include erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk for premature death. Because of the current inability to reliably distinguish tumors that will remain indolent from those destined to be lethal, many men are being subjected to the harms of treatment for prostate cancer that will never become symptomatic.

The benefits of PSA-based screening for prostate cancer do not outweigh the harms.
The harms of prostate cancer screening

• Imperfect test
  – False positives and negatives
  – Risk of diagnostic biopsy
    • In ProtecT, 31.8% reported grade 2 AEs (moderate/major problems) and 1.4% required hospitalization

• Overdiagnosis
  – Estimates of 20-40% of cancers detected by screening on “clinically indolent”
  – Overtreatment

• Side effects of treatment
  – Impotence, incontinence, bowel problems, etc

Etzioni, et al. JNCI 2002
Resnick, et al. NEJM
...BUT WHAT ABOUT THE BENEFITS?
Was the 2012 USPSTF recommendation a foregone conclusion?

THE HISTORY OF USPSTF AND PSA SCREENING
2008 USPSTF Report on PSA Screening

- **Key question #1:** *Does screening for prostate cancer with PSA, as a single threshold test or as a function of multiple tests over time, decrease morbidity or mortality?*
  - ONLY RCTs ALLOWED FOR THIS QUESTION

- **Key Question #2:** *What are the magnitude and nature of harms associated with prostate cancer screening, other than overtreatment?*
  - CROSS-SECTIONAL AND OBSERVATIONAL STUDIES ALLOWED

2008 USPSTF Recommendation on PSA Screening

- Men under age 75: “I” recommendation
  - Waiting for PLCO and ERSPC

- Men over age 75: “D” recommendation
  - Report cites early (2005) SPCG-4 results as the reason men over age 75 should not be screened
What the 2008 recommendation really told us...

- The process was broken even then
  - Limiting which study designs could be used for which questions biased the evidence reviews
- The key questions themselves could be possibly be manipulated
  - Harms of overtreatment not included in the harms of screening in 2008 report
- The general tone of the report implies that unless PLCO and ERSPC were strongly positive, PSA screening was getting a “D”
Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriele, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S., Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D., for the PLCO Project Team*

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*
In 2009, USPSTF immediately began an new evidence review after release of PLCO and ERSPC results

Ultimately published in 2011 Annals of Internal Medicine ahead of USPSTF recommendation (very unusual)

Why?
Clinical Guidelines Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force

Effects of Mammography Screening Under Different Screening Schedules: Model Estimates of Potential Benefits and Harms
The ORIGINAL USPSTF Recommendation

• Recommends against routine screening mammography in women aged 40 to 49 years. The decision to start regular biennial screening in women under age 50 should be an individual one and take into account patient context, including the patient’s values regarding specific benefits and harms. (C)

• Recommends biennial screening mammography for women aged 50 to 74 years. (B)

• Recommends against teaching breast self-examination (BSE). (D)

• Concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in woman over age 75 (I).
Scientific Response to USPSTF: vigorous opposition

• Numerous publications pointing out the problems with the USPSTF’s science
• Focus on incorrect numbers and assumptions
• Problems with modeling studies.
Patient Advocacy Groups Drove the Opposition

• All expressed outrage and opposition
• Pushed elected officials to action
  – House and Senate Committees scheduled hearings on the new guidelines
• Bernadine Healey, first woman to head NIH, said lives could be at risk urged women to ignore the guideline
• Secretary Sebelius stated that women should continue to get regular mammograms starting at age 40
December 4, 2009-less than 1 month after release

- USPSTF “unanimously voted to update the language of their recommendation regarding women less than 50 years of age to clarify their original and continued intent”

- “Decision to start regular, biennial screening mammography before age 50 should be an individual one and take patient context in account, including patient’s values regarding specific benefits and harms”
Why didn’t USPSTF respond to opposition to PCa recommendations?

• Most vocal opponent was AUA:
  – “The AUA is outraged and believes that the Task Force is doing men a great disservice by disparaging what is now the only widely available test for prostate cancer, a potentially devastating disease.”

• Prostate Cancer Roundtable was “disappointed” with the recommendation.
Why did the USPSTF recommendation stand?

• Lack of a strong, coordinated effort on the part of patient advocacy groups to get recommendation overturned

• Weaker media response that was generally sympathetic

• Lack of support from other professional societies and ACS

• Perception that urologists have a financial interest in the outcome and are conflicted.
What now?

So now what do we do with it?
HHS Nominee Tom Price Targeted Panel That Urged Fewer Cancer Screenings

After a task force of experts said evidence didn’t support some cancer screenings, it became the target of lawmakers, including Price and others with health industry ties. Now the critics are in power.

by Marshall Allen
ProPublica, Feb. 1, 2017, 5 a.m.
THE IMPACT OF USPSTF
Impact of USPSTF Recommendation in SEER

Trends in NCDB data by risk-stratum

Is Metastatic disease on the rise?: Results from NCDB 2004-2013

Figure 1. Annual incidence of prostate cancer based on the NCCN risk group relative to 2004 in the United States. Joinpoint regressions were used to model linear trends and determine statistical significance. Trend 1 represents an initial best fit line, whereas trend 2 represents a second linear fit if there is a change in trend from the initial line. The incidence of metastatic prostate cancer has increased recently by 72%, whereas the incidence of low-risk prostate cancer decreased by 37%. APC, annual percentage change; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer.

Weiner et al, PCPD, 2016
Is Metastatic disease on the rise?: Results from NAACCR 2004-2013

NAACCR is population-based and covers 97% of US population

http://news.naaccr.org/rate-of-metastatic-prostate-cancer-is-not-increasing/
Figure. Standardized Incidence of Prostate Cancer Distant Metastasis at Diagnosis by Quarter Between 2004 and 2013 Among Men Aged 75 Years and Older and Younger Than 75 Years

Dashed vertical blue lines demonstrate the release of the 2008 and 2012 screening recommendations.
Figure 2. Delay-Adjusted Incidence (per 100 000 Men) and Incidence Ratio for Distant Prostate Cancer by Age Group, Surveillance, Epidemiology, and End Results 18, 2005-2013

The Pendulum Swings Back and Forth…

how do we stop it in the middle?
REDUCE THE HARMS OF SCREENING
Increasing Use of Observation in SEER-Medicare

Figure 2. Predicted probability of observation for localized prostate cancer by risk, age and CCI groups, and diagnosis year calculated with other model variables set to white race, married status, Western region and median census tract income $38,898 to $56,002.

Ritch, J Urol, 2015
Increasing Use of Observation in SEER

Weiner, J Urol, 2015
Thomas Bayes and Smarter Screening

\[ P(H|DX) = \frac{P(H|X) \times P(D|HX)}{P(D|X)} \]
## Differences in ERSPC protocols

<table>
<thead>
<tr>
<th>Site</th>
<th>Start age</th>
<th>Stop age</th>
<th>Screening Interval</th>
<th>PSA Biopsy threshold</th>
<th>Significant findings?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>55</td>
<td>74</td>
<td>4-7 yrs</td>
<td>10.0 (1&lt;sup&gt;st&lt;/sup&gt; 3 yrs) 4.0 (last 3 yrs)</td>
<td>no</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>55</td>
<td>74</td>
<td>4 yrs</td>
<td>4.0 (1&lt;sup&gt;st&lt;/sup&gt; 3 years) 3.0 (last 3 years)</td>
<td>YES</td>
</tr>
<tr>
<td>Goteborg</td>
<td>50</td>
<td>69</td>
<td>2 yrs</td>
<td>3.0 (1&lt;sup&gt;st&lt;/sup&gt; 3 years) 2.5 (last 3 years)</td>
<td>YES</td>
</tr>
<tr>
<td>Finland</td>
<td>55</td>
<td>71</td>
<td>4 yrs</td>
<td>4.0 (with other factors)</td>
<td>no</td>
</tr>
<tr>
<td>France</td>
<td>55</td>
<td>69</td>
<td>2 yrs</td>
<td>3.0</td>
<td>no</td>
</tr>
<tr>
<td>Spain</td>
<td>55</td>
<td>74</td>
<td>4 yrs</td>
<td>3.0</td>
<td>no</td>
</tr>
<tr>
<td>Italy</td>
<td>55</td>
<td>74</td>
<td>4 yrs</td>
<td>4.0</td>
<td>no</td>
</tr>
<tr>
<td>Switzerland</td>
<td>55</td>
<td>75</td>
<td>4 yrs</td>
<td>3.0</td>
<td>no</td>
</tr>
</tbody>
</table>
Prostate Cancer Risk Nomograms

• The use of a nomogram to identify men at higher risk for prostate cancer who need to undergo screening and biopsy makes sense
  – Application of Bayesian principles
  – Would reduce number of biopsies and harm of screening

• In reality, will be a challenge to implement
  – Clinicians are not always adept at the application of nomograms, particularly complex nomograms
  – Once a patient knows his PSA, can he ignore it?
PSA predicts risk of death and metastases at a later age

• Case-control study of 21,277 Swedish men who provided a blood sample from 1974-84
  – 44% of later prostate cancer deaths occurred in men in the highest decile of PSA
  – Men 45-49 with a PSA >1.6 had a 5.14% risk of dying of prostate cancer within 25 years
  – PSA was more effective in men of older ages

• Problems
  – Would providers and patients be willing to reduce or withhold further screening in men with a PSA <1.6?

PSA at age 60 predicts prostate cancer incidence and outcome:
1756 men in Goteborg study and 1162 men in Malmo study

<table>
<thead>
<tr>
<th>Cumulative incidence (%)</th>
<th>Baseline total PSA level (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-0.99</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Population based centile*</td>
<td></td>
</tr>
<tr>
<td>Gothenburg cohort</td>
<td>&lt;39</td>
</tr>
<tr>
<td>Malmö cohort</td>
<td>&lt;44</td>
</tr>
<tr>
<td>Prostate cancer diagnosis:</td>
<td></td>
</tr>
<tr>
<td>Gothenburg cohort</td>
<td>3.6</td>
</tr>
<tr>
<td>Malmö cohort</td>
<td>1.9</td>
</tr>
<tr>
<td>Prostate cancer metastasis:</td>
<td></td>
</tr>
<tr>
<td>Gothenburg cohort</td>
<td>0.4</td>
</tr>
<tr>
<td>Malmö cohort</td>
<td>0.0</td>
</tr>
<tr>
<td>Prostate cancer death:</td>
<td></td>
</tr>
<tr>
<td>Gothenburg cohort</td>
<td>0.2</td>
</tr>
<tr>
<td>Malmö cohort</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Cumulative incidences were calculated using the Kaplan-Meier method.
*Centiles can be used to find the percentage of men in each PSA category at age 60.

Authors conclude no further screening is needed in men over age 60 with a PSA <1.0

A routine screening interval of 2yrs or more may be preferred over annual screening in those men who have participated in shared-decision making and chosen screening. As compared to annual screening, it is expected that screening intervals of 2yrs preserve the majority of benefits and reduce over diagnosis and false positives (Option; Evidence Grade: C)

Intervals for rescreening can be individualized by a baseline PSA level and/or prior PSA history
Table 1. Indications for biopsy in men with PSA ≥ 3 ng/mL

<table>
<thead>
<tr>
<th>Indication</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>The PSA level</td>
<td>Risk of aggressive prostate cancer continues to increase with PSA; a man with a PSA of 8-10 ng/mL commonly has higher risk of a clinically significant cancer than a man of the same age with a PSA of 3-4 ng/mL.</td>
</tr>
<tr>
<td>Results of the digital rectal examination</td>
<td>Nodularity would clearly be an indication for biopsy; enlargement might suggest benign disease.</td>
</tr>
<tr>
<td>Age and comorbidities</td>
<td>Due to the strong association between age and overdiagnosis, there should be a greater propensity to biopsy men with longer life expectancy.</td>
</tr>
<tr>
<td>Race</td>
<td>African Americans have a higher risk of high-grade disease than men of other races.</td>
</tr>
<tr>
<td>Changes in PSA</td>
<td>A recent sudden rise in PSA is often associated with benign disease.</td>
</tr>
<tr>
<td>Repeat PSA</td>
<td>Some men with elevated PSA will have PSA fall below biopsy thresholds on repeat PSA a few weeks later.</td>
</tr>
<tr>
<td>Reflex tests</td>
<td>Commercially available reflex tests—tests that are used if a first test is positive—that have been shown to be associated with the risk of high-grade disease include blood tests such as the free-to-total PSA ratio, the Prostate Health Index, the 4Kscore, and the urinary testing of PCA3.</td>
</tr>
<tr>
<td>Prior biopsy</td>
<td>A prior negative biopsy lowers the risk of aggressive disease.</td>
</tr>
<tr>
<td>Workup and treatment of benign disease</td>
<td>Patients with symptoms of benign prostate disease, such as urinary urgency, are less likely to have prostate cancer for a given PSA level.</td>
</tr>
<tr>
<td>Use of 5-α reductase inhibitors</td>
<td>Interpretation of measured PSA level needs to take into account medications that affect PSA levels.</td>
</tr>
<tr>
<td>Patient preference</td>
<td>Some patients are more averse to invasive procedures, such as prostate biopsy, than others, and so a higher overall risk of aggressive cancer might be required to indicate biopsy.</td>
</tr>
</tbody>
</table>

...but this is expert opinion only

• Used data from control arm of PCPT and SEER
• Modeled 35 different screening strategies
  – Varied stop and start age, screening interval and threshold for biopsy (absolute level and velocity)
• Assessed NND and found that with lifetime follow-up in some cases, NND could be as 2.99
• Model suggests biennial screening strategy with longer intervals in men with low PSA coupled with higher thresholds for biopsy in older men
Cost-Effectiveness of Prostate Cancer Screening: Data from ERSPC: 68 strategies tested

Screen every other year from 55-59 and then stop with a biopsy threshold of 3.

Prostate Cancer Screening: What now?

• Acknowledge that NO ONE is suggesting population-wide screening
  – No more screening vans and health fairs
  – Shared decision-making

• Explore collaborative ways to SCREEN SMARTER

• Accept alternative study designs to identify the best ways to screen

• Urologists need to accept that they may have to take on a much bigger role in prostate cancer screening
  – This will not be surgical
  – It will not reimburse well