The balance of harms and benefits of screening for prostate cancer: the apples and oranges problem solved

Harold C. Sox, MD, MACP
The Patient-Centered Outcomes Research Institute
April 2, 2016
Declarations

Harold Sox is an employee of PCORI but is not representing PCORI policy at this meeting.

He has no conflicts of interest to declare.
Funding Streams at PCORI

• “Broad” Funding Announcement:
  – Topics chosen by the investigator

• Pragmatic Clinical Studies Funding Announcement:
  – Topics chosen by PCORI and its stakeholders

• Targeted Funding Announcement:
  – Topics chosen by PCORI and its stakeholders
**Funding Streams at PCORI**

- **“Broad” Funding Announcement**
  - Investigator-initiated; up to $2M and 3 years
  - Based on the 5 broad national priorities

- **Pragmatic Clinical Studies Funding Announcement:**
  - Lists ~25 PCORI High Priority Topics. Choose one or propose a topic; up to $10M over 3-5 years.
  - 3 cycles per year; observational or randomized;

- **Targeted Funding Announcement:**
  - Lists one topic chosen by PCORI; may have multiple research questions; funding varies
    - (HCV: up to $50M; four research questions).
Pathway to a Funding Announcement

1. Staff use Tier 1 and Tier 2 review criteria to determine topic eligibility, producing List 1.

2. Science Oversight Committee (SOC) reviews and endorses topics for topic briefs, producing List 2.

3. SOC reviews topic briefs and approves them for Advisory Panel review, producing List 3.


5. SOC reviews AP results and staff recommendations; endorses topics for further refinement, producing List 5.

6. Staff and SOC use Tier 4 review criteria to assess research questions; SOC assigns research questions to targeted or Pragmatic Clinical Studies PFA; producing Lists 6 and 7.

7. Board reviews/approves questions for targeted PFAs.

8. SOC reviews and approves questions for Pragmatic Clinical Studies PFA.
Priority Setting Criteria

- Patient-centeredness
- Burden of illness
- Evidence gaps
- What do guidelines say?
- Ongoing studies
- Likelihood of implementation in practice
- Likely durability of research results
- Proposed research questions
AUA-nominated topics in PCORI topic development pathway

• Management of kidney stones:
  – diet and drugs

• BPH:
  – Comparative effectiveness of lifestyle changes, diet modification, behavioral interventions and phytotherapy on the clinical symptoms of BPH

• Castration-resistant prostate cancer
Prostate Cancer screening
# Prostate cancer screening GLs in the U.S.

<table>
<thead>
<tr>
<th>Source</th>
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<th>Recommendation</th>
</tr>
</thead>
<tbody>
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<td>2012</td>
<td>Do not do it</td>
</tr>
<tr>
<td>U of Michigan</td>
<td>2011</td>
<td>Discuss at age 50</td>
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All agree that men with life expectancy <10 years shouldn’t be screened
Current AUA guidelines

- Age <40-54: do not screen average risk men. (C)
- Age 40-54: do not routinely screen average risk men (C)
  - shared decision making for those at higher risk.
- Age 55-69: shared decision making (B)
- Age 70+: do not screen routinely (C)
- Addenda:
  - Do not screen men with <10-15 year life expectancy
  - Screening every other year (C)
# Prostate cancer screening GLs in the U.S.

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All agree that men with life expectancy <10 years shouldn’t be screened.
Which of these guidelines shall I choose?

• Which one can I trust to rely on the scientific evidence?

• Which one is the most objective in assessing the balance of harms and benefits?
My interests in guidelines

• Creating a market for high quality guidelines
  – Many guidelines for a topic; varying quality
  – Need a metric of quality to help users choose the most trustworthy guideline.

How to Decide Whether a Clinical Practice Guideline Is Trustworthy

David F. Ransohoff, MD
Michael Pignone, MD, MPH
Harold C. Sox, MD

favorable balance of harms and benefits and should therefore become recommended practice. Because benefits and harms are often measured in different units, quantitative estimation of net benefit is necessarily subjective and therefore potentially

JAMA. 2013;309:139-40.
About Guidelines

• They have become powerful because they influence many aspects of practice.
  – Insurance coverage
  – Practice measures
  – Quality of care improvement goals

• The recommendations are susceptible to bias
  – Conflict of interest
  – Selective use of evidence
  – Subjectivity in assessing the balance of harms and benefits is largely unavoidable.
Guideline recommendations of the National Academy of Medicine

• Manage panel members’ and sponsors’ conflicts of interests
• Do a systematic review of the evidence
• Describe the logic that connects the evidence to the recommendation
• Describe the magnitude of the benefits and harms and discuss the balance between them → recommendations.
The process for making a guideline

1. Choose topic
2. Form guidelines panel
3. **Define key questions**
4. Do a systematic review of the evidence for each key question
5. Panel makes recommendations

---

Harms
Benefits
Analytic framework and key questions (KQs)

The process for making a guideline

Choose topic

↓

Form guidelines panel

↓

Define key questions

↓

Do a systematic review of the evidence for each key question

Panel makes recommendations

Harms

Benefits
The US Preventive Services Task Force on prostate cancer screening

Evidence and recommendations

2011-2012
2011-12 US Preventive Services Task Force Recommendation for Prostate Cancer screening.

– Benefits:
  • Treatment: surgery > watchful waiting in <65 year olds
  • Screening: 2 controlled trials of PSA screening
    – US trial: no effect on prostate cancer mortality
    – European trial: 22% reduction in PC mortality

– Harms
  • Urinary incontinence: ↑ 18-28 percentage points by surgery
  • Erectile Dysfunction: ↑ 26-36 percentage points by surgery
Assessment of Harms and Benefits of Screening for Prostate Cancer

• In its recommendation statement, the USPSTF said: “Assessing the balance of benefits and harms requires weighing a moderate to high probability of persistent harm from treatment against the low probability of preventing a death from prostate cancer in the long-term”

• “The USPSTF concludes that there is moderate certainty that the benefits of PSA-based screening for prostate cancer do not outweigh the harms.”
2011-12 US Preventive Services Task Force Recommendation for Prostate Cancer screening.

– Conclusion:
  • “reduction in PC mortality is at most very small; harms of screening and treatment are common and often persistent. Moderate certainty that benefits of screening do not outweigh harms.”

– Recommendation:
  • Recommend against screening
Options for weighing the balance of harms and benefits

• Look at a table of outcomes, their frequency with and without screening, and a description of the health states \(\rightarrow\) a subjective judgment.
  – The preferred approach for an individual patient
  – Such tables appear in many decision aids
  – The patient’s choice is utility-maximizing.

• Given the variation in a population, making a subjective estimate of the balance of harms and benefits for a population is hard to imagine as an instrument for policy-making. But it happens.
## Screening outcomes: 60 year old man*

<table>
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<tr>
<th>Outcome</th>
<th>Effect (vs. no screening)</th>
<th>Units</th>
</tr>
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<tbody>
<tr>
<td>Prostate cancer cured, if present</td>
<td>Longer life</td>
<td>Years gained; QOL</td>
</tr>
<tr>
<td>Anxiety relieved</td>
<td>Happier</td>
<td>Better QOL for rest of life</td>
</tr>
<tr>
<td>Prostate biopsy</td>
<td>Pain for a few days; anxiety</td>
<td>Reduced QOL for few days</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Pads or diaper</td>
<td>% needing pad/diapers</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Less sex</td>
<td>% w/ worse erectile function</td>
</tr>
<tr>
<td>Bowel dysfunction</td>
<td>Unpredictable urge to.....</td>
<td>% w/ poor bowel function</td>
</tr>
<tr>
<td>Over-diagnosis</td>
<td>In those with adverse effects of Rx, chagrin at knowing Rx might not have been needed</td>
<td>Reduction in QOL, adverse effects of treatment</td>
</tr>
</tbody>
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*Life expectancy 21.0 years*
Benefits:
Treatment: surgery > watchful waiting in <65 year olds
Screening: 2 controlled trials of PSA screening
  US trial: no effect on prostate cancer mortality
  European trial: 22% reduction in PC mortality

Harms
Urinary incontinence: ↑18-28 percentage points by surgery
Impotence: ↑26-36 percentage points by surgery
Options for using outcomes data to decide whether to recommend screening

• Look at a table of outcomes, their frequency with and without screening, and a description of the health states → a subjective judgment.

• Create a model that uses a common metric to quantitate the gains and losses from screening.
  – Heijnsdijk et al: used quality-adjusted life years (QALYs) as a common metric for benefits and harms in their microsimulation model.
    • QALY: time in a health state x quality of life in it

Original Article

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.

N Engl J Med
Volume 367(7):595-605
August 16, 2012
My interests in guidelines

• Finding objective methods to estimate net benefits (i.e. benefits minus harms)
  – Reduce subjectivity/bias in assessing balance of H and B
  – Take account of patient’s preferences for the outcome states that they may experience

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Quality of Life and Guidelines for PSA Screening
Harold C. Sox, M.D.

What the Dutch model does

• Simulates life history of a person
• At any time, chance events may occur:
  – A patient may develop a prostate nodule or an elevated PSA (or the PSA may continue to be normal)
  – The prostate biopsy may positive (or not)
  – The patient may choose surgery, radiation, or active surveillance (a choice, not a chance)
  – Treatment may be curative or not
  – The patient may develop complications of treatment (or not)
• Using a computer, a large number of cases can be created very quickly
  – Depending on chance, events may occur early, later, or not at all → a distribution of life expectancies.
• Screening compared to no screening → difference in outcomes
Screening

- Age 60
  - PSA yearly
  - PSA+
  - Bx+
  - surgery
  - Urine/sex Sx
  - 6 yrs
  - Good health

- Age 70
  - 8 yrs
  - Ok save for Urinary Sx
  - 4 yrs
  - Going downhill
  - 18 yrs

- Age 80
  - Cancer death
  - Other death

Note: Ok save for Urinary Sx means the condition remains the same or slightly improves, but may still require ongoing monitoring.
Screening

6 + 0.9 \times 8 + 0.7 \times 4 = 16 \text{ quality-adjusted years}
No Screening 6 + 0.9 \times 4 + 0.7 \times 4 = 12.4 \text{ quality-adjusted years}
Modeling outcomes of prostate cancer screening

• Generate 1000 cases like the examples
  – The probabilities of transition between health states come from the literature → how long each case stays in a health state → a distribution of lengths of time in the state.
  – The distribution of utilities for the health states come from the literature.

• The result is a distribution of lengths of time in the various health states and utilities for those health states → distribution of QALYS.
No. of patients

Serum concentration

Fig. 5-1
<table>
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<th>Utility for health state (best, worst case estimate)</th>
<th>Duration of health state</th>
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<td>0.99 (1.0-0.99)</td>
<td>1 wk</td>
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<tr>
<td>Biopsy</td>
<td>0.90 (0.94-0.87)</td>
<td>3 wk</td>
</tr>
<tr>
<td>Cancer diagnosis</td>
<td>0.80 (0.85-0.75)</td>
<td>1 mo</td>
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<tr>
<td>Radiation Rx</td>
<td>0.73 (0.91-0.71) 0-2 mos 0.78 (0.88-0.61) 2-12 mos</td>
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<tr>
<td>Radical prostatectomy</td>
<td>0.67 (0.90-0.56) 0-2 mos 0.77 (0.91-0.70) 2-12 mos</td>
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<td>Active surveillance</td>
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<td>Post-recovery period</td>
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<td>Palliative Rx</td>
<td>0.60 (0.24-0.86)</td>
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<td>Terminal illness</td>
<td>0.40 (0.24-0.40)</td>
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Suppose you are indifferent between the gamble and the sure thing when $p[\text{death}]$ is 0.10. Then,

$$U[\text{Class IV Angina}] = .10 \times 0 + .90 \times 1.0 = .90$$
Utilities for Angina Pectoris

Nease et al.  
*JAMA* 1995;273:1185-90
QUALITY-ADJUSTED LIFE EXPECTANCY

QUALITY-ADJUSTED LIFE EXPECTANCY = LIFE EXPECTANCY \times UTILITY FOR AN OUTCOME STATE

LIFE IN CLASS IV ANGINA

= 20 YEARS \times 0.90

= 18 HEALTHY YEARS (QALYs)
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Table 3. Effect of Various Health States with and without Annual Screening for Prostate Cancer over the Lifetime of 1000 Men between the Ages of 55 and 69 Years. *

<table>
<thead>
<tr>
<th>Health State</th>
<th>Utility Loss</th>
<th>No Screening</th>
<th>Screening</th>
<th>Difference between Screening and No Screening</th>
<th>Quality Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no. of men</td>
<td>no. of life-yr†</td>
<td>no. of life-yr (range)‡</td>
<td></td>
</tr>
<tr>
<td>Screening attendance</td>
<td>-0.01</td>
<td>0</td>
<td>8242</td>
<td>158</td>
<td>-1.6 (-1.9 to -0.3)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>-0.10</td>
<td>313</td>
<td>605</td>
<td>17</td>
<td>-1.7 (-2.2 to -1.0)</td>
</tr>
<tr>
<td>Cancer diagnosis</td>
<td>-0.20</td>
<td>112</td>
<td>157</td>
<td>4</td>
<td>-0.7 (-0.9 to -0.6)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 mo after procedure</td>
<td>-0.27</td>
<td>43</td>
<td>48</td>
<td>1</td>
<td>-0.2 (-0.2 to -0.1)</td>
</tr>
<tr>
<td>At &gt;2 mo to 1 yr after procedure</td>
<td>-0.22</td>
<td>43</td>
<td>48</td>
<td>4</td>
<td>-0.9 (-1.6 to -0.5)</td>
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<tr>
<td>Radical prostatectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 mo after procedure</td>
<td>-0.33</td>
<td>32</td>
<td>68</td>
<td>6</td>
<td>-2.0 (-2.7 to -0.6)</td>
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<tr>
<td>Active surveillance</td>
<td>-0.03</td>
<td>28</td>
<td>48</td>
<td>106</td>
<td>-3.2 (-15.8 to 0)</td>
</tr>
<tr>
<td>Postrecovery period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No overdiagnosis</td>
<td>-0.05</td>
<td>75</td>
<td>71</td>
<td>109</td>
<td>-5.5 (-36.4 to 0)</td>
</tr>
<tr>
<td>Overdiagnosis</td>
<td>-0.05</td>
<td>0</td>
<td>45</td>
<td>215</td>
<td>-10.8 (-30.3 to 0)</td>
</tr>
<tr>
<td>Palliative therapy</td>
<td>-0.40</td>
<td>40</td>
<td>26</td>
<td>-35</td>
<td>14.1 (5.1 to 26.9)</td>
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<tr>
<td>Terminal illness</td>
<td>-0.60</td>
<td>31</td>
<td>22</td>
<td>-4</td>
<td>2.6 (2.6 to 3.3)</td>
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* The rate of attendance at screenings was assumed to be 80%. The total adjustment in the number of life-years owing to all health effects was -16.7 (range, -93.8 to 24.4).
† The difference in the number of men who underwent screening and those who did not undergo screening has been multiplied by the duration of the health states (as shown in Table 1).
‡ The difference in life-years for each health state has been multiplied by the utility loss to calculate the adjustment for quality of life.

<table>
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<tr>
<th>Health state</th>
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<th>No Screening</th>
<th>Screening</th>
<th>Screen minus No Screen (No. men)</th>
<th>Screen minus No Screen (No. life-years)</th>
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Utility for biopsy = 0.90

No. men who develop Sx of prostate CA --> Bx

Excess Bx due to screening

Men with PSA >3 or 4 ng/ml → Bx

3 wks in Post-Bx state = .06 yrs × 292 = 17 yrs

Utility loss × No. life-years = -0.1 × 17 = -1.7

Denominator: 1000 screened men aged 55-69 years
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Men who develop Sx of prostate CA

Men with PSA >3 or 4 ng/ml

Excess Bx due to screening

3 wks in Bx state = .06 yrs
X 292 = 17

Utility loss x No. life-years
-0.1 x 17 = -1.7

**Interpretation:** in 1000 screened men 55-69 years old, prostate biopsy results in a loss of 1.7 quality-adjusted (i.e., healthy) years of life.
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<tr>
<td>Active surveillance</td>
<td>0.97</td>
<td>-3.2 (-15.9 to 0)</td>
</tr>
<tr>
<td>Post-recovery period</td>
<td>0.95</td>
<td>-5.5 (-36.4 to 0) no overdiagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-10.8 (-30.3 to 0) overdiagnosis</td>
</tr>
<tr>
<td>Palliative Rx</td>
<td>0.60</td>
<td>+14.1 (+5.1 to +26.9)</td>
</tr>
<tr>
<td>Terminal illness</td>
<td>0.40</td>
<td>+2.6 (+2.6 to +3.3)</td>
</tr>
</tbody>
</table>

Total adjustment for health effects of Rx = -16.7 QALYs (range, -93.8 to +24.4)
Quality-adjusted life-years (QALYs)

-100  Lose QALYs  0  Gain QALYs  +100

Net effects: -21 to +97 QALYs

Adjustment for health effects
-93 to +24 QALYS

+ Survival effects (+72.7 QALYs)
# Net effects of screening

<table>
<thead>
<tr>
<th>Effect</th>
<th>QALYs per 1000 men 55-69 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival effects: Life-years (assumes all health states have a utility of 1.0) gained from screening (vs. not screening)</td>
<td>+72.7</td>
</tr>
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<td>Adjustment for health effects of screening</td>
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<tr>
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What does this result say about screening policy?
# Net effects of screening

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What does this result say about screening policy?

Some gain and some lose from prostate cancer screening. **The same recommendation for everyone is not appropriate.**
Effect of Various Modeling Assumptions on Quality-Adjusted Life Years (QALYs) Gained by Prostate Cancer Screening in Comparison with the Base Model.

Net benefit (quality adjusted years/1000 screened men)
Net benefit (quality adjusted years/1000 screened men)

Screen no one

Lose

Gain

-100

0

+100
Net benefit (quality adjusted years/1000 screened men)

- Lose
- Gain

Shared decision-making

Screen All

Screen no one
### Prostate cancer screening GLs in the U.S.

<table>
<thead>
<tr>
<th>Source</th>
<th>Date</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Preventive Services Task Force</td>
<td>2012</td>
<td>Do not do it</td>
</tr>
<tr>
<td>U of Michigan</td>
<td>2011</td>
<td>Discuss at age 50</td>
</tr>
<tr>
<td>American Cancer Society</td>
<td>2010</td>
<td>Discuss at age 50</td>
</tr>
<tr>
<td>American Urological Association</td>
<td>2009</td>
<td>Discuss at age 40</td>
</tr>
<tr>
<td>American College of Preventive Medicine</td>
<td>2008</td>
<td>Discuss; don’t screen if patient defers to physician</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>1997</td>
<td>Discuss at age 50</td>
</tr>
<tr>
<td>American Academy of Family Physicians</td>
<td>2008</td>
<td>Discuss</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>?</td>
<td>PSA at age 40</td>
</tr>
<tr>
<td>American Society for Clinical Oncology</td>
<td>2012</td>
<td>Discuss</td>
</tr>
</tbody>
</table>

All agree that men with life expectancy <10 years shouldn’t be screened
The approach taken here is a solution to the problem of estimating net benefit.

It would remove much of the subjectivity involved in making recommendations for guidelines.

A decision support system based on this model could help to individualize screening recommendations.
Conclusions

• The balance of benefits and harms of an intervention are a touchstone for decision making.

• Benefits and harms are usually measured in different units → hard to assess the balance in close calls.

• Benefits and harms can be expressed as their impact on length and quality of life (QALYs).
Conclusions

- Depending on their utilities for adverse effects of treatment, prostate cancer patients may gain or lose QALYs by undergoing PSA screening.

- At a population level, this means that shared decision making is the preferred intervention for prostate cancer screening.

- At an individual level, patients need to make up their own minds about the downstream health states –> SHARED DECISION MAKING
  - Their likelihood
  - Their meaning for their lives