CONTROVERSIES IN PSA SCREENING

Why the controversy?

Randomized trials.

Recommendations from organizations.
Why The Controversy?

- PSA originally introduced as a tumor marker to detect disease recurrence after therapy and to monitor effect of treatment.

- PSA became adopted for prostate cancer screening in the absence of studies demonstrating its efficacy for this purpose.
Why The Controversy?

- Harms and costs associated with screening and treatments that occur as a result of screening.

- Two large randomized studies had conflicting results and several factors that impact how the results are interpreted.

- Several organizations have developed recommendations that are varying and sometimes conflicting.
Randomized Trials

- United States - PLCO (Prostate, Lung, Colon, and Ovarian Cancer Screening Trial)
- Europe - ERSPC (European Randomized Study of Screening for Prostate Cancer)

- Initiated in the early 1990’s to determine whether PSA-based screening results in a reduction in prostate cancer related mortality.
From 1993-2001, men and women, ages 55-74, enrolled at 10 centers across the U.S.

Exclusion: history of a PLCO cancer, current cancer treatment, starting in 1995-having had more than one PSA test in prior 3 years.

PLCO

- Annual PSA for 6 years and annual DRE for 4 years.
- PSA >4.0 ng/mL was considered positive.
- If positive PSA or abnormal DRE, diagnostic evaluation was decided by the patients and their PCP’s.

PLCO

- **Primary Endpoint**: Cause-specific mortality for each of the PLCO cancers.

- **Secondary Endpoints**: Cancer incidence, staging, and survival.

### Characteristics of the Subjects at Baseline.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Screening Group (N = 38,343)</th>
<th>Control Group (N = 38,350)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>percent</td>
<td>percent</td>
</tr>
<tr>
<td>Age</td>
<td></td>
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</tr>
<tr>
<td>55–59 yr</td>
<td>32.3</td>
<td>32.3</td>
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<tr>
<td>60–64 yr</td>
<td>31.3</td>
<td>31.3</td>
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<tr>
<td>65–69 yr</td>
<td>23.2</td>
<td>23.2</td>
</tr>
<tr>
<td>70–74 yr</td>
<td>13.2</td>
<td>13.2</td>
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<tr>
<td>Race or ethnic group†</td>
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<td></td>
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<tr>
<td>Non-Hispanic white</td>
<td>86.2</td>
<td>83.8</td>
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<tr>
<td>Non-Hispanic black</td>
<td>4.5</td>
<td>4.3</td>
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<tr>
<td>Hispanic</td>
<td>2.1</td>
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<tr>
<td>Asian</td>
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<tr>
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<td>0.9</td>
</tr>
<tr>
<td>Missing data</td>
<td>2.4</td>
<td>5.0</td>
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<tr>
<td>Enlarged prostate or benign prostatic hyperplasia</td>
<td>21.4</td>
<td>20.5</td>
</tr>
<tr>
<td>Previous prostate biopsy</td>
<td>4.3</td>
<td>4.3</td>
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<tr>
<td>Family history of prostate cancer</td>
<td>7.1</td>
<td>6.7</td>
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<tr>
<td>PSA test within past 3 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once</td>
<td>34.6</td>
<td>34.3</td>
</tr>
<tr>
<td>Two or more times</td>
<td>9.4</td>
<td>9.8</td>
</tr>
<tr>
<td>Digital rectal examination within past 3 yr</td>
<td></td>
<td></td>
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<tr>
<td>Once</td>
<td>32.8</td>
<td>31.9</td>
</tr>
<tr>
<td>Two or more times</td>
<td>22.2</td>
<td>22.0</td>
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</table>

* PSA denotes prostate-specific antigen.
† Race or ethnic group was self-reported.
Compliance with screening protocol was 85% for PSA testing and 86% for DRE.

Control group:
- 40% PSA testing in 1\textsuperscript{st} year.
- 52% PSA tested by 6\textsuperscript{th} year.
- DRE 41-46%.

At 10 years, prostate cancer diagnosed:
- 3452 subjects in screened group.
- 2974 subjects in control group.
- Rate ratio 1.17, 95% CI, 1.11-1.22.

At 10 years, prostate cancer deaths:
- 92 subjects in the screened group.
- 82 subjects in the control group.
- Rate ratio 1.11, 95% CI, 0.83-1.50.
Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B).

### Table 2. Tumor Stage, Histopathological Type, and Gleason Score for All Prostate Cancers at 10 Years, According to Method of Detection and Time of Diagnosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Screening Group</th>
<th>Control Group</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All Subjects</td>
<td>All Subjects</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(N=3452)</td>
<td>(N=2974)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Never Screened (N=154)</strong></td>
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<tr>
<td><strong>After Screening (N=875)</strong></td>
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<tr>
<td><strong>Outside of Screening Protocol (N=374)</strong></td>
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<tr>
<td><strong>Screen Detected at Baseline (N=549)</strong></td>
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<tr>
<td><strong>Screen Detected at Yr 1–Yr 5 (N=1500)</strong></td>
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<td></td>
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<tr>
<td><strong>Clinical stage</strong></td>
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<tr>
<td>I</td>
<td>1 (0.6)</td>
<td>5 (0.6)</td>
<td>8 (2.1)</td>
<td>2 (0.4)</td>
<td>2 (0.1)</td>
<td>18 (0.5)</td>
</tr>
<tr>
<td>II</td>
<td>138 (93.6)</td>
<td>838 (95.8)</td>
<td>347 (92.8)</td>
<td>516 (94.0)</td>
<td>1458 (97.2)</td>
<td>3297 (95.5)</td>
</tr>
<tr>
<td>III</td>
<td>5 (3.2)</td>
<td>7 (0.8)</td>
<td>3 (0.8)</td>
<td>12 (2.2)</td>
<td>22 (1.5)</td>
<td>49 (1.4)</td>
</tr>
<tr>
<td>IV</td>
<td>10 (6.5)</td>
<td>20 (2.3)</td>
<td>9 (2.4)</td>
<td>19 (3.5)</td>
<td>15 (1.0)</td>
<td>73 (2.1)</td>
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<tr>
<td>Unknown</td>
<td>0</td>
<td>5 (0.6)</td>
<td>7 (1.9)</td>
<td>0</td>
<td>3 (0.2)</td>
<td>15 (0.4)</td>
</tr>
<tr>
<td><strong>Histopathological type</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Any</td>
<td>144 (93.5)</td>
<td>824 (94.2)</td>
<td>346 (92.5)</td>
<td>511 (93.1)</td>
<td>1375 (91.7)</td>
<td>3200 (92.7)</td>
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<tr>
<td>Acinar</td>
<td>9 (5.8)</td>
<td>48 (5.5)</td>
<td>25 (6.7)</td>
<td>36 (6.6)</td>
<td>124 (8.3)</td>
<td>242 (7.0)</td>
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<tr>
<td>Other</td>
<td>1 (0.6)</td>
<td>3 (0.3)</td>
<td>3 (0.8)</td>
<td>2 (0.4)</td>
<td>1 (0.1)</td>
<td>10 (0.3)</td>
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<tr>
<td><strong>Gleason score on biopsy</strong></td>
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</tr>
<tr>
<td>2–4</td>
<td>11 (7.1)</td>
<td>1.7 (1.9)</td>
<td>36 (9.6)</td>
<td>64 (11.7)</td>
<td>94 (6.3)</td>
<td>222 (6.4)</td>
</tr>
<tr>
<td>5–6</td>
<td>78 (50.6)</td>
<td>500 (57.1)</td>
<td>228 (61.0)</td>
<td>278 (50.6)</td>
<td>963 (64.2)</td>
<td>2047 (59.3)</td>
</tr>
<tr>
<td>7</td>
<td>39 (25.3)</td>
<td>252 (28.8)</td>
<td>74 (19.8)</td>
<td>132 (24.0)</td>
<td>318 (21.2)</td>
<td>815 (23.6)</td>
</tr>
<tr>
<td>8–10</td>
<td>16 (10.4)</td>
<td>95 (10.9)</td>
<td>25 (6.7)</td>
<td>55 (10.0)</td>
<td>98 (6.5)</td>
<td>289 (8.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (6.5)</td>
<td>11 (1.3)</td>
<td>11 (2.9)</td>
<td>20 (3.6)</td>
<td>27 (1.8)</td>
<td>79 (2.3)</td>
</tr>
</tbody>
</table>

* Subjects with available data for tumor staging but not for nodal status or the presence or absence of metastasis were classified as having stage II disease. Percentages may not total 100 because of rounding.

† The Gleason score ranges from 2 to 10, with higher scores indicating more aggressive disease.
Cumulative number of prostate cancers in the intervention and control arms from year 1 to year 13.

RR = 1.12 (1.07-1.17)
Cumulative deaths from prostate cancer in the intervention and control arms from year 1 to year 13.

RR = 1.09 (0.87-1.36)
• Wide confidence intervals.
• ERSPC used lower PSA cutoff.
• High level of contamination (52% by year 6) in control arm in terms of number of subjects who underwent screening.
• ~44% of men in each study group had undergone PSA testing at baseline.
• Improvements in therapy potentially leading to fewer prostate cancer deaths.
ERSPC

- Initiated in early 1990’s
- To determine whether a 25% reduction in prostate cancer mortality could be achieved by PSA-based screening.
- Men age 50-74.
  - Age 55-69 (core age group).
- Most centers used a PSA cutoff of 3.0 ng/mL.

ERSPC

- In Finland, PSA cutoff of 4.0 ng/mL, PSA of 3.0-3.9 ng/mL referred for ancillary testing, and if positive, referred for biopsy.
- In Italy, PSA cutoff of 4.0 ng/mL, PSA of 2.5-3.0 ng/mL referred for ancillary testing.
- In Dutch and Belgian centers, up to 1997, DRE, TRUS, and PSA was used, after 1997, just PSA.

ERSPC

- PSA tested every 4 years, except 2-year interval was used in Sweden.

- In Belgium, interval between first and second screen was 7 years due to an interruption in funding.
Great deal of variability from one country to the next.
Among men assigned to screening, 76% attended first screening.

Among men assigned to control, 31% had at least one PSA test.
Enrollment and Outcomes, According to Age Group at Randomization.

182,160 Subjects 50–74 yr old underwent randomization
162,387 Were in the core age group (55–69 yr old)

160 Subjects 50–74 yr old died
144 Were 55–69 yr old

82,816 Were assigned to the screening group
72,890 Were 55–69 yr old

6830 Had prostate cancer
5990 Were 55–69 yr old

99,184 Were assigned to the control group
89,353 Were 55–69 yr old

4781 Had prostate cancer
4307 Were 55–69 yr old
After 9 years of follow up:

- Rate ratio for death from prostate cancer in the screened group was 0.80 (95% CI, 0.67-0.95, p=0.01).

- Number of men that need to be screened to prevent one prostate cancer death was 1410.

- Number of men that need to be treated to prevent one prostate cancer death was 48.

ERSPC

- In an intention to screen analysis (men who actually underwent screening):
  - Rate ratio for death from prostate cancer was 0.71
  - Number of men needed to screen to prevent one prostate cancer death was 1068.
  - Number of men that need to be treated to prevent one prostate cancer death was 48.

Updated analysis:

- 11 years follow up
  - NNI- 979
  - NNT- 35
- 13 years follow up
  - NNI- 781
  - NNT- 27

PLCO vs. ERSPC

“Why are the results different?”
PLCO vs. ERSPC

- Variations in study protocol from one country to the next in the ERSPC.
  - PLCO had uniform protocol.
- Higher contamination rate in control arm of PLCO
- High number of subjects had undergone PSA testing prior to study entry in PLCO.
  - Number not known in ERSPC.
PLCO vs. ERSPC

- Lower PSA cutoff used in ERSPC vs. PLCO.

- Differential treatment between study and control groups.
  - This was equal in the PLCO.
  - In the ERSPC, a control subject with high-risk disease was more likely than a screen subject to receive radiation (OR: 1.43; 1.01-2.05, p=0.047), expectant management (OR: 2.92; 1.33-6.42, p=0.007), or hormonal therapy (OR: 1.77; 1.07-2.94, p=0.026), instead of prostatectomy.

How is this being interpreted and applied?
Recommendations

- USPSTF
- NCCN (National Comprehensive Cancer Network)
- American Cancer Society
- AUA (American Urological Association)
- ACP
- ASCO (American Society of Clinical Oncology)
USPSTF (2012)

- Recommends against PSA-based screening for prostate cancer.
- Grade D: Moderate or high certainty that the test has no net benefit or the harms outweigh the benefits.

Baseline PSA testing should be offered to healthy, well-informed men aged 45-75 years. May be complemented by DRE.

- Testing every 2-4 years if PSA is <1.0 ng/mL.
- Testing every 1-2 years if PSA is 1.0 ng/mL or greater.
If PSA >3.0 ng/mL, biopsy should be considered, but should incorporate other variables including age, family history, PSA kinetics, race, health status, and patient preference.

PSA testing be considered only in very select men >75 years.

PSA testing not recommended for men unlikely to benefit based on age/comorbidities.
Consideration may be given to biomarkers that improve biopsy specificity such as % free PSA, 4K score, PHI, PCA3 before biopsy in men with PSA >3.0 ng/mL.
Men should have a chance to make an informed decision about being screened.

- Age 50, for average risk men expected to live 10 years or more.
- Age 45, for high risk men (African-American with a first-degree relative with prostate cancer diagnosed age <65).
- Age 40, for higher risk men (more than one first-degree relative with prostate cancer at an early age).

www.cancer.org/cancer/prostatecancer
• PSA <2.5 ng/mL, test every 2 years.
• PSA 2.5 ng/mL or greater, test annually.

• Testing should not be offered to men with a life expectancy <10 years.
Recommends against PSA screening in men <40 years.

Recommends against PSA screening in average-risk men age 40-54 years.

Recommend shared decision making in deciding to screen men age 55-69.
  - Screening interval of 2 years or more
  - Intervals can be individualized by baseline PSA
AUA

- Recommends against routine screening in men 70+ years or with <10-15 year life expectancy.
- Some men age 70+ years in excellent health may benefit.

www.auanet.org/education/guidelines/prostate-cancer-detection.cfm
Recommends against PSA testing in average risk men <50 or >69 years, or life expectancy <10-15 years.

Men age 50-69 years should make an informed decision.
- Recommends against screening in men with life expectancy <10 years.

- For men with a life expectancy 10+ years, they should make an informed decision about screening.
Summary

- Clearly a controversial area.

- Personal perspective:
  - “Blanket approach” to screening the population with PSA testing leads to some saved lives at the expense of the harms of screening and treatment, and unnecessary treatments being performed.
Summary

- Personal perspective:
  - Prostate cancer screening should not be abandoned, but improved.
  - “What can we do?”
Summary

- Personal perspective:
  - “Modified approach” to screening.
    - Be selective in whom we screen.
    - Risk-adapted screening
    - Complementary tests
      - Biomarker/molecular
      - Imaging
  - May decrease the NNT to save a life.
  - Improvements in therapies may also lead to increased cures and further decrease the NNT to save a life.
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