PSA as a prostate cancer screening tool – past, present and future.

Oscar B. Goodman, Jr., M.D., Ph.D.
Nevada Cancer Coalition
Cancer Control Summit
September 16, 2019
Disclosures

• Nothing formal to disclose.

• As a medical oncologist I rarely prescribe primary prostate cancer screening, however I use PSA as a monitoring tool.

• My practice includes men who are with regard to primary PSA screening:
  • True positives
  • False positives
  • False negatives
Objectives

• Describe the historical and present role of PSA testing as a prostate cancer screening tool.

• Characterize the realized clinical impact of decreased PSA testing on the natural history of prostate cancer.
Overview of the talk

• Historical overview of PSA as a biomarker
• Review of PSA screening prospective studies
• Overview of PSA screening guidelines
• PSA screening trends and impact on prostate cancer disease states
• Optimizing PSA screening
Importance of risk-benefit analysis

Sorry I'm late for your digital-rectal exam...
I slammed my finger in my car door.
Historical overview of PSA as a prostate cancer biomarker
PSA (prostate specific antigen)- a brief history

• 1970: Ablin identified PSA while searching for prostate cancer specific antigens released by cryosurgical ablation of prostate tumors.

• 1979: C hu (re)discovered PSA while searching for cancer antigens; ultimately patented as a diagnostic in 1984
1981: Using hybridoma technology Hybritech developed clinically used α-PSA mAb (partnering with Roswell Park).

1986- PSA approved by FDA for monitoring of men who had definitive therapy for prostate cancer.

1986-1994: Widespread off-label use of PSA screening ensues….
Male Cancer Incidence 1975-2015

*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting. †Includes the intrahepatic bile duct.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2019.
PSA- a brief history, continued

• 1987- Stamey et al., NEJM demonstrate PSA more sensitive than PAP in detecting cancer in a cohort with advanced disease.

• 1991- Catalona et al., NEJM propose PSA as a PC screening test.
MEASUREMENT OF PROSTATE-SPECIFIC ANTIGEN IN SERUM AS A SCREENING TEST FOR PROSTATE CANCER

WILLIAM J. CATALONA, M.D., DEBORAH S. SMITH, PH.D., TIMOTHY L. RATLIFF, PH.D., KATHY M. DODDS, R.N., DOUGLAS E. COPLEN, M.D., JERRY J.J. YUAN, M.D., JOHN A. PETROS, M.D., AND GERALD L. ANDRIOLE, M.D.

Table 4. Accuracy of Rectal Examination, Serum PSA Measurement, and Ultrasonography in Detecting Prostate Cancer on First Biopsy in 300 Men in the Comparison Group.

<table>
<thead>
<tr>
<th>Measure*</th>
<th>Rectal Examination</th>
<th>Ultrasonography</th>
<th>Serum PSA†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>86</td>
<td>92</td>
<td>79</td>
</tr>
<tr>
<td>Specificity</td>
<td>44</td>
<td>27</td>
<td>59</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>33</td>
<td>28</td>
<td>40</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>91</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td><strong>58</strong></td>
<td><strong>43</strong></td>
<td><strong>64</strong></td>
</tr>
</tbody>
</table>

*Sensitivity was determined by dividing the number of true positive results by the number of true positives plus the number of false negatives, specificity by dividing the number of true negative results by the number of true negatives plus the number of false positives, positive predictive value by dividing the number of true positive results by the number of true positives and false positives combined, negative predictive value by dividing the number of true negative results by the number of true negatives and false negatives combined, and overall accuracy by dividing the number of true positive and true negative results by the total number tested.

†Values are based on a sample of 235 men (65 patients in the comparison group did not have serum PSA determinations).
PSA- a brief history, continued

Correlation of screening PSA with cancer risk:

<table>
<thead>
<tr>
<th>PSA ng/ml</th>
<th>Risk of prostate cancer</th>
<th>Risk of aggressive prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>0.6 - 1.0</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>1.1 - 2.0</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>2.1 - 3.0</td>
<td>24%</td>
<td>5%</td>
</tr>
<tr>
<td>3.1 - 4.0</td>
<td>27%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Prostate Cancer Prevention Trial (PCPT)
PSA- a brief history, continued

- 1994- PSA approved by FDA for the early detection of prostate cancer.

- 1996 Percent-free PSA approved by FDA as an adjunctive prostate cancer screening tool.
PSA politics
PSA structure and function

- Human kallikrein-3
- Glycoprotein serine protease.
- Secreted in seminal fluid.
- Facilitates sperm motility and uterine entry.
- Produced by both normal and malignant epithelial cells.
- Transits into circulation.

Regulation of PSA by androgen receptor (AR) signaling

Legend
- **T**: Testosterone
- **D**: Dihydrotestosterone
- **AR**: Androgen receptor
- **PSA mRNA**: PSA messenger RNA
- **PSA**: PSA protein

Diagram:
- Testosterone (T) is converted to Dihydrotestosterone (D) by 5-α-reductase.
- Dihydrotestosterone (D) binds to the Androgen receptor (AR) in the cytoplasm and nucleus.
- The Androgen receptor (AR) binds to the PSA gene, regulating PSA expression.
Clinical sources of PSA variation

• Mechanical perturbation (e.g. truck drivers, DRE)
• Benign prostatic hypertrophy
• Prostatitis/inflammation
• Medications (5-α-reductase inhibitors, anti-inflammatories)*
• Supplements (testosterone, androgenic herbs)

* Since these lower PSA, may impact sensitivity as well
## Occupation and PSA

<table>
<thead>
<tr>
<th></th>
<th>PSA &lt; threshold n (%)</th>
<th>PSA ≥ threshold n (%)</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA threshold 4.0 ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Production workers</td>
<td>1,690 (99.5)</td>
<td>9 (0.5)</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Office workers</td>
<td>251 (96.9)</td>
<td>8 (3.1)</td>
<td>5.98</td>
<td>2.29-15.65</td>
<td>7.73</td>
<td>2.78-21.46</td>
</tr>
<tr>
<td><strong>Age &lt; 50</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Production workers</td>
<td>1,079 (99.6)</td>
<td>4 (0.4)</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Office workers</td>
<td>187 (99.5)</td>
<td>1 (0.5)</td>
<td>1.44</td>
<td>0.16-12.97</td>
<td>2.372</td>
<td>0.24-22.84</td>
</tr>
<tr>
<td><strong>Age ≥ 50</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Production workers</td>
<td>611 (99.2)</td>
<td>5 (0.8)</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Office workers</td>
<td>64 (90.1)</td>
<td>7 (9.9)</td>
<td>13.37</td>
<td>4.13-43.33</td>
<td>12.90</td>
<td>3.65-45.64</td>
</tr>
</tbody>
</table>

*Ann Occup Environ Med. 26: 50 (2014)*
Conclusions: Historical overview of PSA as a biomarker

- PSA has had a controversial history with clinical impact driven by early off label use.
- PSA is tightly regulated by AR signaling, which may be impacted by a variety of factors.
- PSA lacks specificity with many clinical sources of variation.
Review of PSA screening prospective studies
Male cancer-specific mortality-1930-2015

*Age-adjusted to the 2000 US standard population. †Includes intrahepatic bile duct, gallbladder, and other biliary systems.

Note: Due to International Classification of Diseases coding changes, numerator information for colorectal, liver, and biliary system cancer deaths is limited to 1969-1973.

# Overview of PSA screening trials

<table>
<thead>
<tr>
<th>Study</th>
<th>PLCO</th>
<th>ERSPC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>USA</td>
<td>Europe</td>
</tr>
<tr>
<td><strong>Number enrolled</strong></td>
<td>76,693</td>
<td>182,000</td>
</tr>
<tr>
<td><strong>Years enrolled</strong></td>
<td>1993-2001</td>
<td>1991-2003</td>
</tr>
<tr>
<td><strong>Screening interval</strong></td>
<td>annual</td>
<td>2-4 years</td>
</tr>
<tr>
<td><strong>Ages included</strong></td>
<td>55-74</td>
<td>55-69</td>
</tr>
<tr>
<td><strong>PSA Biopsy threshold</strong></td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Control arm PSA contamination</strong></td>
<td>77%</td>
<td>20-25%</td>
</tr>
</tbody>
</table>

PLCO- prostate, lung, colon, ovarian screening

ERSPC- European Randomized study of Screening for Prostate Cancer conducted in Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland
Screening increases early detection of prostate cancer, but . . .

<table>
<thead>
<tr>
<th>Study</th>
<th>US (PLCO screening)</th>
<th>Europe (ERSPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer incidence in unscreened</td>
<td>95/10,000 person-years</td>
<td>49/10,000 person-years</td>
</tr>
<tr>
<td>Cancer incidence in screened</td>
<td>116/10,000 person-years</td>
<td>76/10,000 person-years</td>
</tr>
<tr>
<td>Cancer deaths in unscreened</td>
<td>1.7/10,000 person-years</td>
<td>4.1/10,000 person-years</td>
</tr>
<tr>
<td>Cancer deaths in screened</td>
<td>2.0/10,000 person-years</td>
<td>3.5/ 10,000 person-years</td>
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Impact on prostate cancer-specific survival is mixed

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<td>3.5/10,000 person-years</td>
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Number needed to treat (NNT) = 48
Number needed to screen (NNS) = 1410
In the E RSPC study, screening correlates with a 20% decrease in prostate cancer death rates at 9 year. Assuming $NNS = 1,410$, $NNT = 48$:

- **PSA**  $1,410 \times $50 \times 2$ tests/patient = $141,000$
- **DRE**  $1,410 \times $100 = $141,000$
- **TRUS** $(1,410 \times 0.16 \times $4000/test = $902,400$)
- **Radical Prostatectomy**: $48 \times $12,173 = $584,304$
- **Cost to prevent one PC-specific death**: $1,768,704$
- **Cost to prevent 20% (6,400) of deaths**: $11,319,705,600$

Fraction with PSA $> 3$ ng/mL

http://healthcarebluebook.com/page_Default.aspx
http://EzineArticles.com/6514961
http://ezinearticles.com/?Prostate-Cancer:-The-Dreaded-Prostate-Biopsy-and-Alternatives&id=6514961
Luo JL et al, *Nature. 2007*
http://health.costhelper.com/blood-test.html
The unaccounted costs of biopsy

- Pain and suffering (~100%)
- Sepsis (2%)
- Theoretical concerns for seeding, local inflammation (??)
PSA screening trials: conclusions

- Screening results in the diagnosis of more prostate cancers in both studies.
- In the US (PLCO) study, screening had no impact on reducing prostate cancer death rates, with contamination felt to play a role.
- In the European (ERSPC) study, screening was associated with a 20% risk reduction in prostate cancer deaths.
Overview of PSA Screening Guidelines
Prior USPSTF PSA Screening Policy Statements

2008
• Current evidence is insufficient to assess the balance of benefits and harms of screening for prostate cancer in men younger than age 75 years (Grade C).
• Do not screen for prostate cancer in men age 75 years or older (Grade D).

2012
The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)-based screening for prostate cancer (Grade D).
# Current PSA Screening Guidelines

<table>
<thead>
<tr>
<th>ENTITY</th>
<th>&lt;40</th>
<th>MEN 40-55</th>
<th>55-69</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUA</td>
<td>Against (Grade C)</td>
<td>Against except high risk (Grade C)</td>
<td>Consider (Grade B) Biennial</td>
<td>Against if life expectancy &lt;10-15 years (Grade C) Consider otherwise</td>
</tr>
<tr>
<td>NCCN</td>
<td>No policy</td>
<td>Starting at 45 and based on perceived risk (FH, germline mutations, race, medications) risk stratify based on baseline PSA: • PSA&lt;1, normal DRE: obtain PSA every 2-4 years • PSA 1-3, normal DRE: obtain PSA every 1-2 years • PSA &gt;3 and/or suspicious DRE: biopsy</td>
<td>Healthy and &gt;75: PSA &gt;4: biopsy</td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>No policy</td>
<td>Consider at: • 40 if &gt; 1 first degree relative with PC • 45 if 1 first degree relative &lt;65 or AA • 50 for men at average risk and &gt; 10 years survival • Annual for PSA&gt;2.5, otherwise biennially</td>
<td>Consider</td>
<td>Consider (no age cap in policy)</td>
</tr>
<tr>
<td>USPSTF</td>
<td>No policy</td>
<td>No policy</td>
<td>Consider (Grade C)</td>
<td>Against (Grade D)</td>
</tr>
</tbody>
</table>

**Early Detection of Prostate Cancer: AUA Guideline (2013)**


**NCCN Guidelines: Prostate Cancer Early Detection (2018)**
USPSTF PSA Screening Policy Statement Revised in 2018

For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)–based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening.

The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older.

PSA Screening Summary

• In the last 10+ years guidelines for PSA screening have become increasingly conservative.

• PSA screening recommendations tend to incorporate the biases of recommending entities.

• My opinion: Age is a number. Consider all potential factors (especially race, family history- most closely mirrors NC CN). Counsel patients on risks and benefits of testing.
PSA screening trends and impact on prostate cancer disease states
Rates of PSA screening and biopsy

- Rate of PSA testing
- Rate of TRUS Biopsy

* 2011 public draft of USPSTF recommendations released (no screening)

Rates of prostate cancer detection and treatment

*2011 public draft of USPSTF recommendations released

Figure 2. Changes over time relative to 2011 age-standardized rates for prostate-specific antigen testing, prostate needle biopsy, new diagnoses of prostate cancer, and definitive local therapy for prostate cancer. PSA, prostate-specific antigen.

Prostate Cancer Incidence

*2008- USPSTF states insufficient evidence to support screening

Metastatic Prostate Cancer Incidence as a function of age

Metastatic prostate cancer incidence as a function of age and race

Overall 45-54

55-64 65-74

>75 Race

AA W

Delela et al., European Urology Foc 5:77-80 (2019)
Male cancer-specific mortality-1930-2015

*Age-adjusted to the 2000 US standard population. †Includes intrahepatic bile duct, gallbladder, and other biliary tract cancers.

NOTE: Due to International Classification of Diseases coding changes, numerator information for colorectal, liver, and other cancers previous to 1999 may not be equivalent. Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2018.
Summary - PSA screening trends and impact on prostate cancer disease states

• The incidences of PSA screening, localized disease, and definitive therapy have been decreasing.
• The incidence of metastatic disease has been increasing over the last decade, particularly in populations discouraged from screening.
• There is an apparent correlation between USPSTF recommendations and acceleration of this trend.
• This is not causal proof, however.
• Possible future PC-specific mortality impact.
Optimizing PSA Screening

- Adjunctive tools
  - % free PSA
  - PSA density
  - Urinary PCA3 testing (FDA approved in 2012 for men with prior negative biopsy).
Optimizing PSA Screening

- % Free PSA
- Circulating PSA complexes with $\alpha$-1-antichymotrypsin (to prevent proteolytic inactivation).
- Lower % free PSA increases PSA specificity

Lilija et al., Clin Chem 37/9 1618-1625 (1991)
Southwick, Lab Med 32/5 259-263 (2001)
Table 4.
Multivariate analyses of PSA, PSA density and Gleason score in predicting positive surgical margins, extracapsular disease, seminal vesicle invasion and lymph node invasion

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>Exp(B)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivariate analysis for prediction of PSM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>0.001</td>
<td>0.013</td>
<td>0.004</td>
<td>1</td>
<td>0.947</td>
<td>1.001</td>
<td>0.975</td>
<td>1.028</td>
</tr>
<tr>
<td>PSAD</td>
<td>-0.884</td>
<td>0.264</td>
<td>11.191</td>
<td>1</td>
<td>0.001</td>
<td>0.413</td>
<td>0.246</td>
<td>0.693</td>
</tr>
<tr>
<td>GS</td>
<td>0.265</td>
<td>0.110</td>
<td>5.797</td>
<td>1</td>
<td>0.016</td>
<td>1.303</td>
<td>1.050</td>
<td>1.616</td>
</tr>
<tr>
<td><strong>Multivariate analysis for prediction of ECD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PSA</td>
<td>0.021</td>
<td>0.018</td>
<td>1.294</td>
<td>1</td>
<td>0.255</td>
<td>1.021</td>
<td>0.985</td>
<td>1.058</td>
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<tr>
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<td>-2.042</td>
<td>0.334</td>
<td>37.302</td>
<td>1</td>
<td>0.000</td>
<td>0.130</td>
<td>0.067</td>
<td>0.250</td>
</tr>
<tr>
<td>GS</td>
<td>0.271</td>
<td>0.127</td>
<td>4.506</td>
<td>1</td>
<td>0.034</td>
<td>1.311</td>
<td>1.021</td>
<td>1.683</td>
</tr>
<tr>
<td><strong>Multivariate analysis for prediction of SVI</strong></td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PSA</td>
<td>0.045</td>
<td>0.021</td>
<td>4.744</td>
<td>1</td>
<td>0.029</td>
<td>1.046</td>
<td>1.005</td>
<td>1.089</td>
</tr>
<tr>
<td>PSAD</td>
<td>-1.324</td>
<td>0.456</td>
<td>8.841</td>
<td>1</td>
<td>0.004</td>
<td>0.266</td>
<td>0.109</td>
<td>0.650</td>
</tr>
<tr>
<td>GS</td>
<td>0.238</td>
<td>0.163</td>
<td>2.125</td>
<td>1</td>
<td>0.145</td>
<td>1.269</td>
<td>0.921</td>
<td>1.747</td>
</tr>
<tr>
<td><strong>Multivariate analysis for prediction of LNI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>0.009</td>
<td>0.015</td>
<td>0.389</td>
<td>1</td>
<td>0.532</td>
<td>1.009</td>
<td>0.981</td>
<td>1.038</td>
</tr>
<tr>
<td>PSAD</td>
<td>-2.949</td>
<td>1.044</td>
<td>7.972</td>
<td>1</td>
<td>0.005</td>
<td>0.052</td>
<td>0.007</td>
<td>0.406</td>
</tr>
<tr>
<td>GS</td>
<td>0.432</td>
<td>0.235</td>
<td>3.382</td>
<td>1</td>
<td>0.066</td>
<td>1.540</td>
<td>0.972</td>
<td>2.439</td>
</tr>
</tbody>
</table>
Optimizing PSA screening

- Urinary PCA3 testing
  - A Inc RNA produced by malignant prostate cells (specific).
- Urine collected following DRE
- Prospective prostate cancer screening comparative study (n=201) vs PSA:

<table>
<thead>
<tr>
<th></th>
<th>PSA (&lt;2.5)</th>
<th>PSA (4-10)</th>
<th>PCA3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>98%</td>
<td>84%</td>
<td>82%</td>
</tr>
<tr>
<td>Specificity</td>
<td>5%</td>
<td>80%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Future screening approaches

- Multiparametric MRI- helps detect/target high grade disease
- Nuclear medical imaging of novel prostate-specific antigens
- Novel biomarkers (including PSA-based glycomic markers)
Conclusions

- PSA screening is imperfect but still a standard of care.
- PSA screening appears to save lives, but at a cost.
- Prostate cancer incidence appears to correlate with PSA prescribing practices.
- Adjunctive screening approaches may be helpful, but newer approaches are needed.
Thanks!

Questions?