Screening and Risk Stratification of Men for Prostate Cancer *Metastasis and Mortality*

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Disclosure

• Conflict of interest: None
Prostate Cancer

Ok, who is next?
Goals for Today’s Session

• Current prostate cancer screening practices and challenges for early detection of prostate cancer
• The value of PSA as a sensitive predictor of prostate cancer mortality
• PSA ordering practices of primary care physicians
• What is a reasonable approach to prostate cancer screening?
• Validity, safety and effectiveness of an innovative second stage biomarker test as a follow-up test after an abnormal PSA to identify who should (and should not) receive a prostate biopsy
### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>161,360</td>
<td>252,710</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,990</td>
<td>105,510</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>71,420</td>
<td>64,010</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>60,480</td>
<td>61,380</td>
</tr>
<tr>
<td>Melanoma</td>
<td>52,170</td>
<td>42,470</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,610</td>
<td>34,940</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>40,080</td>
<td>32,160</td>
</tr>
<tr>
<td>Leukemia</td>
<td>36,290</td>
<td>25,640</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>35,720</td>
<td>25,700</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>29,200</td>
<td>23,380</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>836,150</strong></td>
<td><strong>852,630</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>84,590</td>
<td>71,280</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>27,150</td>
<td>40,610</td>
</tr>
<tr>
<td>Prostate</td>
<td>26,730</td>
<td>23,110</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,300</td>
<td>20,790</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>19,610</td>
<td>14,080</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,300</td>
<td>10,820</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,720</td>
<td>10,200</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,240</td>
<td>9,310</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,450</td>
<td>8,690</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,620</td>
<td>7,080</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>318,420</strong></td>
<td><strong>282,500</strong></td>
</tr>
</tbody>
</table>

*FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2017.*

Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.
PROSTATE-SPECIFIC ANTIGEN AS A SERUM MARKER FOR ADENOCARCINOMA OF THE PROSTATE

THOMAS A. STAMEY, M.D., NORMAN YANG, PH.D., ALAN R. HAY, M.D., JOHN E. MCNEAL, M.D., FUAD S. FREIHA, M.D., AND ELISE REDWINE, B.A.

Abstract To compare the clinical usefulness of the serum markers prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), we measured them by radioimmunoassay in 2200 serum samples from 699 patients, 378 of whom had prostatic cancer.

PSA was elevated in 122 of 127 patients with newly diagnosed, untreated prostatic cancer, including 7 of 12 patients with unsuspected early disease and all of 115 with more advanced disease. The PSA level increased with advancing clinical stage and was proportional to the estimated volume of the tumor. The PAP concentration was elevated in only 57 of the patients with cancer and correlated less closely with tumor volume. PSA was increased in 86 percent and PAP in 14 percent of the patients with benign prostatic hyperplasia.

After radical prostatectomy for cancer, PSA routinely fell to undetectable levels, with a half-life of 2.2 days. If initially elevated, PAP fell to normal levels within 24 hours but always remained detectable. In six patients followed postoperatively by means of repeated measurements, PSA — but not PAP — appeared to be useful in detecting residual and early recurrence of tumor and in monitoring responses to radiation therapy.

Prostate massage increased the levels of both PSA and PAP approximately 1.5 to 2 times. Needle biopsy and transurethral resection increased both considerably.

We conclude that PSA is more sensitive than PAP in the detection of prostatic cancer and will probably be more useful in monitoring responses and recurrence after therapy. However, since both PSA and PAP may be elevated in benign prostatic hyperplasia, neither marker is specific.

Lifetime Risk of Prostate Cancer Death

- Death, prostate cancer – 3%
- Diagnosis, prostate cancer – 17%
- No prostate cancer during lifetime – 83%
What do we know from randomized trials?

- Screening Works

- Over-detection is a problem

- An overwhelming number of men are exposed to invasive testing and treatment to save one life
Approaches to Screening: How did we start?

PSA>4.0

Your PSA is Elevated. You need a biopsy.”

PSA<4.0

“Your PSA is Normal. No testing is necessary.”
Population Screening with PSA: The Truth!

<table>
<thead>
<tr>
<th>PSA 4+</th>
<th>7.6%</th>
<th>Screen 10,000 Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive biopsy</td>
<td>25%</td>
<td>PSA 4+ 760</td>
</tr>
<tr>
<td>High grade</td>
<td>19%</td>
<td>Cancer 190</td>
</tr>
<tr>
<td>Normal PSA</td>
<td>92.4%</td>
<td>PSA &lt;4 9240</td>
</tr>
<tr>
<td>Positive biopsy</td>
<td>15%</td>
<td>Cancer 1386</td>
</tr>
<tr>
<td>High grade</td>
<td>15%</td>
<td>High grade 208</td>
</tr>
</tbody>
</table>

SEER, PCAW, Prostate Cancer Prevention Trial Data
USE OF 2.6 NG/ML PROSTATE SPECIFIC ANTIGEN PROMPT FOR BIOPSY IN MEN OLDER THAN 60 YEARS

ROBERT B. NADLER,* † STACY LOEB, KIMBERLY A. ROEHL, JO ANN V. ANTENOR, SCOTT EGGENER AND WILLIAM J. CATALONA‡

From the Department of Urology, Northwestern University, Feinberg School of Medicine (RBN, SL, SE, WJC), Chicago, Illinois, and Departments of Psychiatry (KAR), Neurology (JAVA) and Surgery/Urology (WJC), Washington University, St. Louis, Missouri

LOWERING PSA CUTOFFS TO ENHANCE DETECTION OF CURABLE PROSTATE CANCER

WILLIAM J. CATALONA, CHRISTIAN G. RAMOS, GUSTAVO F. CARVALHAL, AND YAN YAN
What are the risk of screening?

Prostate Biopsy?
Prostate Biopsy

- Increasing trend of quinolone resistant sepsis
- Urinary Complications
- Costs
- Emotional Stress

- Up to 75% of biopsies negative for cancer or show low risk – unlikely to affect quantity/quality of life
Under and Over Treatment

Cooperberg et al. J Clin Oncol 2010; 28:1117
Public Health Impact

- Patient awareness of overtreatment
- Controversy regarding detection and treatment
Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, PhD, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2008 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for prostate cancer.

Methods: The USPSTF reviewed new evidence on the benefits and harms of prostate-specific antigen (PSA)-based screening for prostate cancer, as well as the benefits and harms of treatment of prostate cancer.

Recommendation: The USPSTF recommends against PSA-based screening for prostate cancer (grade D recommendation).

This recommendation applies to men in the general U.S. population, regardless of age. This recommendation does not include the use of the PSA test for surveillance after diagnosis or treatment of prostate cancer; the use of the PSA test for this indication is outside the scope of the USPSTF.


For author affiliation, see end of text.

* For a list of the members of the USPSTF, see Appendix 1 (available at www.annals.org). This article was published at www.annals.org on 22 May 2012.
Early Detection & Treatment of Aggressive Prostate Cancer is Essential

Widespread PSA Screening leads to Reduced Diagnoses of Metastatic Disease

In response to over diagnosis and over treatment concerns, guidelines against PSA screening were published: rise in patients presenting with metastatic disease.

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To Your Health

The federal panel that opposed prostate cancer screening just changed its mind

By Laurie McGinley  April 11  Email
What Should We Do?

• Screen Smarter – Earlier, less often in elderly

• Screen for aggressive disease – minimize further testing in men who are low risk for significant Pca

• Disconnect Diagnosis and Treatment
Trends in Active Surveillance: Utilization


Cooperberg M et al, JAMA. 2015;314(1):80-82 From 7% to 40%

Loeb S (Sweden): AS in 91% VLR and 74% LR, URS 2015

Weerakoon M (Australia): BJUI 2015: 115 S5, 50-56
What Should We Do?

• Screen Smarter – Earlier, less often in elderly

• Screen for aggressive disease – minimize further testing in men who are low risk for significant Pca

• Disconnect Diagnosis and Treatment
PSA Screening for Prostate Cancer

• Biomarker PSA is an excellent screening test for prostate cancer - sensitive (93%)*
• But - Poor specificity (24%)*
• Inadequate differentiation between indolent and aggressive prostate cancer
• Leads to over-diagnosis and over-treatment

* At 3 ng/mL cut-off
Many Factors Affect PSA Levels

- Age (increase)
- Race (African American > Caucasian)
- Prostate Volume (~4% increase per mL)
- Androgens (lower in hypogonadal men)
- Obesity (lower due to hemodilution)
- Assay (use same assay for serial measurements)
- Medications (anti-inflammatories, statins, 5ARI)
- Genetic Factors (several SNPs associated with PSA)
- Benign Prostatic Conditions (BPH, infection)
- Urinary Tract Manipulation (ex: catheter, cysto)

**Limited Specificity**

*Downstream Harms including unnecessary biopsies with potential associated risk*
1. PSA for screening
2. Follow up biomarker test to detect risk of *Aggressive* Prostate Cancer
   - Identify men with a high risk of Aggressive Prostate Cancer who would benefit from further evaluation and treatment
   - Avoid prostate biopsies in men with a low risk of Aggressive Prostate Cancer to avoid unnecessary complications such as sepsis and overtreatment
Baseline PSA

Age 45-75 y

- PSA < 1 ng/mL, DRE normal (if done)
  - Repeat testing at 2-4 year intervals

- PSA 1-3 ng/mL, DRE normal (if done)
  - Repeat testing at 1-2 year intervals

- PSA > 3 ng/mL, Or very suspicious DRE
  - See Indications for Biopsy

Age > 75 y, in select patients

- PSA < 4 ng/mL, DRE normal (if done), and no other indications for Biopsy
  - Repeat testing in select patients at 1-4 year intervals

- PSA ≥ 4 ng/mL or very suspicious DRE
  - See Indications for Biopsy

- Not Screened
Repeat PSA
- DRE if not performed during initial risk assessment
- Workup for benign disease

Consider biomarkers that improve the specificity of screening
- Or
- Consider multiparametric MRI

Transrectal ultrasound (TRUS)-guided biopsy
Follow-up in 6-12 mo with PSA/DRE

Management of Biopsy Results

“…there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define the probability of high-grade cancer. A percent-free PSA <10%, PHI >35, or 4Kscore (which provides an estimate of the probability of high-grade prostate cancer) are potentially informative in patients who have never undergone biopsy or after a negative biopsy;”
Diagnostic Shift: Sensitivity to Specificity

Early Risk Detection of Clinically Significant Prostate Cancer
Secondary Biomarker Specificity

- Specific in identifying men at risk of having aggressive prostate cancer
- Improve decision making by developing a personalized treatment plan
- Identify a man at risk for high-grade cancer who would benefit from a prostate biopsy
- Identify men at low risk who may judiciously avoid a prostate biopsy but continue to be followed
- Avoid overtreatment of men with indolent prostate cancer
Molecular Markers for Prostate Cancer Detection

4Kscore®
A DIAGNOSTIC BLOOD TEST FOR DETECTING THE RISK OF AGGRESSIVE PROSTATE CANCER

PCA3 TEST
PROSTATE CANCER SCREENING

phi test
prostate health index

UNIVERSITY OF MIAMI HEALTH SYSTEM
Multi-Parametric MRI of the Prostate

T2W

Tumor

Hematoma

DCE

DWI
• 1,012 men prospectively enrolled in 26 academic & community practices
• All subjects underwent minimum 10 core prostate biopsy after blood drawn for 4Kscore Blood drawn prior to biopsy
• Outcomes of biopsy and 4Kscore Test were compared

• 8 Veterans Affairs Hospitals
• 56% of the 366 men are African American
4Kscore Prospective Validation Trials

Initial prospective validation

Prospective VA validation

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![Graph showing the results of initial prospective validation and prospective VA validation with the title "4Kscore Prospective Validation Trials" and the subtitle "Initial prospective validation" for the left graph and "Prospective VA validation" for the right graph. The graphs illustrate the relationship between predicted and actual biopsy results for a dataset of 1012 patients.]
Results of Combined Two Clinical Validation Studies

4Kscore US Validation and VA Studies
N = 1378

• Sensitivity 94%
• NPV 95%

4Kscore <7.5%
N = 444 (32.2%)

Neg.
N = 338
(76.1%)

GS 6
N = 85
(19.1%)

GS 3+4
N = 15
(3.4%)

GS 4+3
N = 6
(1.4%)

GS ≥8
N = 0
(0%)

Missed No Gleason ≥8

4Kscore ≥7.5%
N = 934 (67.8%)

Neg.
N = 355
(38.0%)

GS 6
N = 238
(25.5%)

GS 3+4
N = 152
(16.3%)

GS 4+3
N = 70
(7.5%)

GS ≥8
N = 119
(12.7%)

Data from Parekh et al. Eur Urol 2015 and Punnen et al. J Urol 2018

*(Clinical Performance is illustrated using a 4Kscore 7.5% Cut Point)*
2432 Men Age 60 years old, PSA ≥ 3.0 ng/mL

PSA ≥ 3 ng/mL and 4Kscore < 7.5%: Safe for 5 to 10 years out with no need for further procedure, except recommended PSA screening in between

1822 Men Age 60-73 years old, PSA ≥ 2.0 ng/mL

PSA ≥ 2 ng/mL and 4Kscore < 7.5%: Safe for 5 to 10 years out with no need for further procedure, except recommended PSA screening in between
Multi-Parametric MRI for Prostate Cancer Detection
Multi-Parametric MRI for Prostate Cancer Detection
# MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MRI-Targeted Biopsy Group (N = 252)</th>
<th>Standard-Biopsy Group (N = 248)</th>
<th>Difference†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat analysis — no. (%)</td>
<td>95 (38)</td>
<td>64 (26)</td>
<td>12 (4 to 20)</td>
<td>0.005</td>
</tr>
<tr>
<td>Modified intention-to-treat analysis — no./total no. (%)</td>
<td>95/245 (39)</td>
<td>64/235 (27)</td>
<td>12 (3 to 20)</td>
<td>0.007</td>
</tr>
<tr>
<td>Per-protocol analysis — no./total no. (%)</td>
<td>92/235 (39)</td>
<td>62/227 (27)</td>
<td>12 (3 to 20)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinically insignificant cancer — no. (%)</td>
<td>23 (9)</td>
<td>55 (22)</td>
<td>-13 (-19 to -7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study


575 men underwent mpMRI followed by TPM & TRUS biopsy

- 230 (40%) diagnosed with Gleason ≥4+3
- mpMRI sensitivity 93% & specificity 41%
- 70% with high risk MRI found to have high grade cancer (HGC)

- 11% with low risk MRI found to have HGC
- 21% with indeterminate risk MRI with HGC

Ahmed et al. Lancet 2017
Review – Prostate Cancer


Fig. 3 – Negative predictive value of prebiopsy multiparametric MRI as a function of cancer prevalence (blue crosses: overall prostate cancer; red crosses: clinically significant prostate cancer). The blue line is the correlation line for overall prostate cancer; the red dotted line is the correlation line for clinically significant prostate cancer. mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging.
Biomarkers for Prostate Cancer Detection

• **PRO**
  - Good accuracy for prostate cancer detection
  - Access shouldn’t be an issue
  - Non-Invasive
  - Objective measure of risk

• **Con**
  - Cost
  - Not helpful for targeting
  - Generalizability, cut-offs?
MRI for Prostate Cancer Detection

• **PRO**
  - Good accuracy for detecting clinically significant disease
  - Helpful for targeting
  - Appears to trump all other markers when positive

• **Con**
  - 10-25% of significant cancer seen in non-suspicious MRI’s
  - Access/Cost
  - Reader variability
MRI and 4Kscore for Significant Prostate Cancer Detection

49/149 (33%) men had Gleason 7+ cancer

4Kscore +MRI: AUC - 0.82 (0.73-0.91)
 vs MRI alone: AUC - 0.75 (0.65-0.84), p=0.004
 vs 4Kscore alone: AUC - 0.70,(0.6-0.8), p=0.02

Punnen et al.
Summary:

- PSA is an excellent screening test for prostate cancer, but it lacks specificity.

- Need to screen smarter and for aggressive disease, not any prostate cancer.

- Role of secondary imaging or molecular markers to decide on the need for a biopsy of the prostate (4Kscore, PHI, SelectMDx, PCA3, multi-parametric MRI).

- Disconnect diagnosis and treatment and apply risk adjusted management.
Clarifying the Prostate Biopsy Decision

PSA SCREENING

BIOPSY CANDIDATES

SECONDARY BIOMARKER
Appendix
Secondary biomarkers are indicated for men considering prostate biopsy and meet the following criteria:

1. Abnormal PSA and/or DRE
2. Prostate biopsy naïve or a prior negative biopsy
3. Age 45-75
4. Age 75 - 80 with a life expectancy >10 years
5. Family history of prostate cancer in at least one affected first-degree relative (father or brother), or known BRCA1, BRCA2 gene mutation