Prostate cancer screening: a wobble Balance

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Epidemiology

- Most common non skin malignancy in men in developed countries
- Third leading cause of cancer related death in men
- Pca: 9.6% of new cancer cases in USA
- Incidence : 120 cases/100000 men/year
- Lifetime risk :11.6%
- Median age at diagnosis: 66
- Death : 20 cases/100000 men/year
Number of New Cases per 100,000 Persons by Race/Ethnicity: Prostate Cancer

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>119.8</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>112.8</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>188.7</td>
<td></td>
</tr>
<tr>
<td>Asian / Pacific Islander</td>
<td>62.9</td>
<td></td>
</tr>
<tr>
<td>American Indian / Alaska Native</td>
<td>59.9</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>98.3</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>123.3</td>
<td></td>
</tr>
</tbody>
</table>

SEER 18 2010–2014, Age-Adjusted
Population at risk of prostate cancer → Screening →
1. No prostate cancer
2. Early detection of prostate cancer

Harms of screening

3. Treatment
   - Surgery
   - Radiation therapy
   - Hormonal therapy
   - Cryotherapy
   - Ultrasonography
   - Watchful waiting
   - Active surveillance

4. Harms of treatment

Reduced prostate cancer-specific and all-cause mortality
PSA

- PSA: discovery late 80s and FDA in 1994
- Gamma-seminoprotein or KLK-3
- Race specific normal range:

<table>
<thead>
<tr>
<th>Age Range</th>
<th>PSA Level (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 to 49 years old</td>
<td>0 to 2.0 (blacks); 0 to 2.5 (whites)</td>
</tr>
<tr>
<td>50 to 59 years old</td>
<td>0 to 4.0 (blacks); 0 to 3.5 (whites)</td>
</tr>
<tr>
<td>60 to 69 years old</td>
<td>0 to 4.5 (blacks); 0 to 3.5 (whites)</td>
</tr>
<tr>
<td>70 to 79 years old</td>
<td>0 to 5.5 (blacks); 0 to 3.5 (whites)</td>
</tr>
</tbody>
</table>

- PSA

Se: 21% any Pca / 51% High grade
Sp: 91%
PPV: 30% NPV: 85%

Se: 32% any Pca / 68% High Grade
Sp: 85%
When in the gray zone

PSA density

Re-examining Prostate-specific Antigen (PSA) Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy.

Jue JS¹, Barboza MP¹, Prakash NS¹, Venkatramani V¹, Sinha VR¹, Pavan N², Nahar B¹, Kanabur P¹, Ahdoott M¹, Dong Y³, Satyanarayana R¹, Parekh DJ¹, Punnen S⁴.

CONCLUSION: As PSA increases, PSA density becomes a better marker for predicting prostate cancer compared with PSA alone. Additionally, PSA density performed better than PSA in men with a prior negative biopsy.
PSA velocity

- A cutoff of 0.75ng/ml/yr
Sp: 90% Pca v/s 60% for tPSA >4ng/ml

- If PSA < 4ng/ml and Velocity > 0.35ng/ml/yr >>> High risk of death from Pca 15 years later (3 consecutive PSA tests)

- A PSA velocity > 3 ng/ml/yr >> Prostatic inflammation
Free/Total PSA

- Increase of cancer detection rate from 25% to 56% when the ratio is < 10%

>>> 25% as a cutoff for biopsy

>>> decrease by 20% the need to biopsy

BUT 8% of men have Pca with normal ratio
Digital rectal exam (DRE)

- 2 to 3% of men 50 yo or more >> abnormal DRE
- Se : 59 %
- Sp: 94%
- PPV: 5 to 30%

Combining DRE and PSA:
Detection rate: 3.2% DRE, 4.6% PSA, 5.8% combined

If normal PSA and abnormal DRE>> PPV 10%
If abnormal PSA and normal DRE >> PPV 24%
Evidence of Screening

- PLCO trial
  1. 10 US centers
  2. 76,693 men randomized aged between 55 and 74
  3. PSA cutoff 4 ng/ml
  4. 10 years of follow-up

>> Cancer detection in the screening group > control group

BUT Similar Pca specific mortality even after 14.8 years Follow-up
PLCO trial flaws

- Significant rates of screening in the control arm
  >> 52% Contamination (men were screened prior to study)

- Low rates of biopsy in men who had abnormal screening results in the screening arm
  >> less than 50% of were biopsied
**ERSPC trial:**

1. 7 European centers in different countries
2. 182,160 men between 50 and 74 yo randomized
3. PSA cutoff from 2.5 to 4 ng/ml (3 ng/ml +)
4. Follow up for 13 years

>> To prevent 1 Pca death > screen 781 patients and detect 27 Pca patients

>> 21% reduction Pca mortality only for men aged between 55 and 69 Yo

>> After adjustment of contamination (Rotterdam site data):
   Reduction by 31% of Pca specific mortality
ERSPC Flaws

- Numerous sites of trial entry (7 countries)

- Mortality reduction of 20% came with large investment
<table>
<thead>
<tr>
<th>Years of follow-up</th>
<th>Number needed to screen</th>
<th>Number needed to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1,410</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>979</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>781</td>
<td>27</td>
</tr>
</tbody>
</table>

With extended follow-up:

- Same mortality reduction
- NNS and NNT are decreasing
- NNS for Pca < NNS for breast cancer
Göteborg Screening trial

- 20,000 men randomized
- Age 50-64 included (median 56)
- Median follow-up 14 years

>> 44% reduction in Pca specific death in screened group
>> To prevent 1 death : 293 should be screened and 12 men should be treated

INTERPRETATION: This study shows that prostate cancer mortality was reduced almost by half over 14 years. However, the risk of over-diagnosis is substantial and the number needed to treat is at least as high as in breast-cancer screening programmes. The benefit of prostate-cancer screening compares favourably to other cancer screening programs.
2012 US PREVENTIVE SERVICES TASK FORCE (USPSTF) GUIDELINES

- **GRADE D** recommendation against PSA screening

Per 1000 men screened:

1. 1 fewer prostate cancer death
2. 20% and 30% risk of UI and ED due to treatment
3. 3% risk of CV events and death
PSA screening in US declined following 2012 USPSTF

- National health interview Survey:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>2010</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-74</td>
<td>36.8%</td>
<td>29.9%</td>
</tr>
<tr>
<td>≥75</td>
<td>43.1%</td>
<td>36.3%</td>
</tr>
</tbody>
</table>
Harms of traditional screening

Limited specificity of PSA

- Unnecessary prostate biopsy
- Biopsy complications

- Over diagnosis and treatment
- Unnecessary side effects

2
3
### Harms of screening: Biopsy complications

<table>
<thead>
<tr>
<th>Harms of biopsy</th>
<th>Proportions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria/ Hematospermia</td>
<td>Mean=50.86%</td>
</tr>
<tr>
<td>Infection</td>
<td>Mean= 5-7%</td>
</tr>
<tr>
<td>Hospitalization for infection</td>
<td>1-3%</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>30%</td>
</tr>
<tr>
<td>LUTS</td>
<td>6-25 %</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Death</td>
<td>0.17%</td>
</tr>
</tbody>
</table>
Increasing infectious complications after prostate biopsy due to antimicrobial resistance
2017 NCCN Guidelines

When to recommend an initial Biopsy:
- PSA >3 ng/ml (age > 45)
- PSA ≥ 4 ng/ml (age > 60)
- Very suspicious DRE
Prostate health index (phi)

- Total PSA, free PSA, \([-2] \text{ProPSA}\)

- Reduce unnecessary prostate biopsies for men with PSA between 3 and 10 ng/ml
A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer.

- Four Kallikrein assays (total PSA, free PSA, intact PSA, human kallikrein–related peptidase 2)
- Blood test combined with age and DRE findings

CONCLUSION: The 4Kscore showed excellent diagnostic performance in detecting significant PCa. It is a useful tool in selecting men who have significant disease and are most likely to benefit from a prostate biopsy from men with no cancer or indolent cancer.

PATIENT SUMMARY: The 4Kscore provides each patient with an accurate and personalized measure of the risk of Gleason ≥7 cancer to aid in decision-making regarding the need for prostate biopsy.
Prior negative biopsy

- Atypia, suspicious for cancer:
  - Follow-up:
    - Consider serum or urine tests and/or multiparametric MRI
  - Multifocal (>2 sites):
    - Consider repeated biopsy with relative increased sampling of the atypical site

- High-grade prostatic intraepithelial neoplasia (PIN):
  - Follow-up:
    - PSA and DRE at 6-24 month interval
    - Consider percent free PSA, 4Kscore, PHI, PCA3, or ConfirmMDx and/or multiparametric MRI and/or refined prostate biopsy techniques

- Focal
  - Repeat prostate biopsy, based on risk

- Benign
  - Repeat prostate biopsy, based on risk
PCA3

- Discovered in 1999, overexpressed in Pca tissue specimen but not in normal tissue

- PCA3 score: ratio PCA3 mRNA/ PSA mRNA

- After vigorous DRE >>> URINE TEST

- Guide Biopsy when PSA between 2.5 and 10 ng/ml or after negative biopsy and high PSA

- Sensitivity: 53 to 84%  Specificity: 71 to 80%

- Inferior to phi for predicting aggressive disease

- 2012: FDA approved for men with prior negative biopsy
### Recommendations

In order to avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a prostate specific antigen level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools:

- risk-calculator;
- an additional serum or urine-based test (e.g. Prostate Health Index test [PHI], four kallikrein [4K]score or Prostate cancer gene 3 [PCA3]) or imaging.
Epigenetic changes associated with Pca

> Hypermethylation of 3 markers (GSPT1, APC, RASSF1)

Field effect around a cancer lesion can be present despite normal appearance under a microscope

Absence of methylation changes helps rule out malignancy (NPV 90%) VS histopathology alone (NPV 75%)

Sen: 68%  Sp: 64%

Not FDA approved
Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score.

Van Neste L\textsuperscript{1}, Hendriks RJ\textsuperscript{2}, Dijkstra S\textsuperscript{2}, Trooskens G\textsuperscript{3}, Cornel EB\textsuperscript{4}, Jannink SA\textsuperscript{3}, de Jong H\textsuperscript{3}, Hessels D\textsuperscript{3}, Smit FP\textsuperscript{3}, Melchers WJ\textsuperscript{5}, Leyten GH\textsuperscript{6}, de Reijke TM\textsuperscript{7}, Vergunst H\textsuperscript{8}, Kil P\textsuperscript{9}, Knipscheer BC\textsuperscript{10}, Hulsbergen-van den Kaa CA\textsuperscript{11}, Mulders PF\textsuperscript{2}, van Oort IM\textsuperscript{2}, Van Criekinge W\textsuperscript{12}, Schalken JA\textsuperscript{13}.

SelectMDX

- Reverse transcriptase – PCR on mRNA levels of HOXC6 and DLX1 biomarkers
- First void-urine specimens post DRE
- Creat a risk score including HOXC6 and DLX1 with other clinical factors (age, PSA, Family history, DRE, PSAD, ...)

CONCLUSIONS: The risk score based on the mRNA liquid biopsy assay combined with traditional clinical risk factors identified men at risk of harboring high-grade PCa and resulted in a better patient risk stratification compared with current methods in clinical practice. Therefore, the risk score could reduce the number of unnecessary prostate biopsies.
Multiparametric MRI

- When high quality MRI is available, it should be strongly considered for any patient with a prior negative biopsy considering re-biopsy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before repeat biopsy, perform multiparametric magnetic resonance imaging (mpMRI) when clinical suspicion of PCa persists in spite of negative biopsies.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>During repeat biopsy, include systematic biopsies and targeting of any mpMRI lesions seen.</td>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>
RESULTS: The panel recognizes that many options exist for men with a previously negative biopsy. If a biopsy is recommended, prostate magnetic resonance imaging and subsequent magnetic resonance imaging targeted cores appear to facilitate the detection of clinically significant disease over standardized repeat biopsy. Thus, when high quality prostate magnetic resonance imaging is available, it should be strongly considered for any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy. The decision of whether to perform magnetic resonance imaging in this setting must also take into
Can we exclude Biopsy if MRI is negative?


<table>
<thead>
<tr>
<th></th>
<th>NPV (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CaP</td>
<td>82% (69-92%)</td>
</tr>
<tr>
<td>Significant CaP</td>
<td>88% (86-92%)</td>
</tr>
</tbody>
</table>

CONCLUSIONS: The NPV of mpMRI varied greatly depending on study design, cancer prevalence, and definitions of positive mpMRI and csPCa. As cancer prevalence was highly variable among series, risk stratification of patients should be the initial step before considering prebiopsy mpMRI and defining those in whom biopsy may be omitted when the mpMRI is negative.
Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study.


PROMIS trial

27% reduction for primary biopsy

MP-MRI guided Biopsy: 18% more clinically significant cases

INTERPRETATION: Using MP-MRI to triage men might allow 27% of patients avoid a primary biopsy and diagnosis of 5% fewer clinically insignificant cancers. If subsequent TRUS-biopsies were directed by MP-MRI findings, up to 18% more cases of clinically significant cancer might be detected compared with the standard pathway of TRUS-biopsy for all. MP-MRI, used as a triage test before first prostate biopsy, could reduce unnecessary biopsies by a quarter. MP-MRI can also reduce over-diagnosis of clinically insignificant prostate cancer and improve detection of clinically significant cancer.
Overdiagnosis

- When cancer is detected correctly, BUT would not cause symptoms or death during the patient’s lifetime

- Rate according to ERSPC: 40-56%
Reducing Harms: Overtreatment

- Historically, the vast majority of low risk patients received radical treatment.
- Up to 67% cases overdiagnosed depending on the population and criteria.
ProtecT trial

- 1643 men with localized prostate cancer randomized
- Median age: 62 years
- Median PSA level: 4.6 ng/ml
- Follow-up: 10 years
All-Cause Mortality (per 1000 person-years)

- Active Monitoring: 10.9
- Prostatectomy: 10.1
- Radiotherapy: 10.3
Prostate-Cancer-Specific or All-Cause Mortality

Active Monitoring ≈ Prostatectomy ≈ Radiotherapy

Loeb S¹,², Folkvalljon Y³, Curnyn C¹,², Robinson D⁴,⁵, Bratt O⁶,⁷, Stattin P⁵,⁸.
### Screening Guidelines

- **EAU guidelines**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status and a life-expectancy of at least ten to fifteen years.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Offer early PSA testing in well-informed men at elevated risk of having PCa:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- men &gt; 50 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- men &gt; 45 years of age and a family history of PCa;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- African-Americans &gt; 45 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- men with a PSA level of &gt; 1 ng/mL at 40 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- men with a PSA level of &gt; 2 ng/mL at 60 years of age.</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- men with a PSA level of &gt; 1 ng/mL at 40 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- men with a PSA level of &gt; 2 ng/mL at 60 years of age;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postpone follow-up to eight years in those not at risk.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Decide on the age at which early diagnosis of PCa should be stopped based on life expectancy and performance status; men who have a life-expectancy of &lt; 15-years are unlikely to benefit.</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>
### AUA guidelines

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>Against routine screening</td>
</tr>
<tr>
<td>40-54</td>
<td>Does not recommend routine screening for average-risk. Individual decisions for high-risk</td>
</tr>
<tr>
<td>55-69</td>
<td>Shared decision-making about PSA screening</td>
</tr>
<tr>
<td>70+</td>
<td>Does not recommend routine screening for 70+ or anyone with &lt;10-15y life expectancy</td>
</tr>
</tbody>
</table>

*Grade C* for all age groups.
<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 55-69</td>
<td>Recommends that clinicians inform men about the potential benefits and harms of screening</td>
<td>C</td>
</tr>
<tr>
<td>Age ≥70</td>
<td>Recommends against PSA-based screening</td>
<td>D</td>
</tr>
</tbody>
</table>
Shared Decision Making
Mass screening

Opportunistic testing
THANK YOU