When to Use Prostate Cancer Biomarkers
Which Ones?

UCLA State-of-the-Art Urology Conference

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Baltimore, MD

Disclosure – Genprobe/Hologics, Exosome, Beckman, MDxHealth (Investigator)

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## Biomarker Tests

<table>
<thead>
<tr>
<th>Who to biopsy</th>
<th>Who to re-biopsy</th>
<th>Who to treat vs surveillance</th>
<th>Who to offer adjuvant tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>PCA3</td>
<td>Oncotype DX</td>
<td>Decipher</td>
</tr>
<tr>
<td>PCA3</td>
<td>ConfirmMDx</td>
<td>Prolaris</td>
<td>Prolaris</td>
</tr>
<tr>
<td>PHI</td>
<td></td>
<td>Decipher biopsy</td>
<td></td>
</tr>
<tr>
<td>4K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXO106</td>
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</tr>
</tbody>
</table>

**Will not discuss**

4K, Select MDx, Apifiny, or Gene Panel Tests
Higher $\phi$ values associated with increased risk

<table>
<thead>
<tr>
<th>$\phi$</th>
<th>&lt;25</th>
<th>25-34.9</th>
<th>35-54.9</th>
<th>&gt;55</th>
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</thead>
<tbody>
<tr>
<td>% Prob. PCa</td>
<td>11</td>
<td>18</td>
<td>33</td>
<td>52</td>
</tr>
</tbody>
</table>

- $\Phi_i > 55$ had a 52% probability of PCa
PHI for prediction of Significant cancers

The Prostate Health Index Selectively Identifies Clinically Significant Prostate Cancer
J Urol. 2015 193:1163-9

ALL Epstein Significant GS > 7

<table>
<thead>
<tr>
<th>ALL</th>
<th>Epstein Significant</th>
<th>GS &gt; 7</th>
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</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph A" /></td>
<td><img src="image2.png" alt="Graph B" /></td>
<td><img src="image3.png" alt="Graph C" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>AUC</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
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<tbody>
<tr>
<td>PSA</td>
<td>0.516</td>
<td>0.472 - 0.560</td>
<td>Ref.</td>
</tr>
<tr>
<td>[-2]proPSA</td>
<td>0.550</td>
<td>0.506 - 0.594</td>
<td>0.194</td>
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<tr>
<td>%PSA</td>
<td>0.648</td>
<td>0.606 - 0.690</td>
<td>&lt;0.001</td>
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<tr>
<td>PHI</td>
<td>0.708</td>
<td>0.686 - 0.747</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P-value for PSA vs. [-2]proPSA, %PSA, or PHI
Prostate Health Index (PHI) Predicts High-Stage Pathology in African-American Men

Area under ROC curves
- Reference
- Baseline (DRE): 0.602
- Baseline + %p2PSA: 0.739
- Baseline + PSA: 0.635
- Baseline + PHI: 0.750

Urology. 2016 Apr;90:136-40
PCA3 Urine Assay Procedure

Digital Rectal Exam (3 strokes per lobe) → Urine Specimen

PCA3 and PSA mRNA concentrations measured in separate tubes

Quantitative ratio of PCA3/PSA mRNA = PCA3 Score

PCA3 Score < cutoff → Lower risk of positive biopsy
PCA3 Score ≥ cutoff → Higher risk of positive biopsy

PCA3: a molecular urine assay for predicting prostate biopsy outcome.

Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H, Groskopf J.
Gen-Probe, Inc., San Diego, California 92121, USA.
**Initial Biopsy:** High Positive Predictive Value (PPV) @ PCA3 score > 60

- PPV 80% (95%CI 0.72 – 0.86)
- If cancer is present, PCA3 will be positive 80% of the time

**Repeat Biopsy:** High Negative Predictive Value (NPV) @ PCA3 score < 20

- NPV 0.88 (95%CI 0.81 – 0.93)
- If cancer is not present, PCA3 will be negative 88% of the time
Potential application

PSA Screening
Prostate DRE

Elevated PSA
Abnormal DRE

Biopsy
Pathology

Negative Histology

Prostate ConfirmMDx

Repeat Biopsy

continued routine screening
ConfirmMDx (MDxHealth)

- Evaluates DNA hypermethylation in benign tissue from a prior negative biopsy
  - 3 genes: APC, GSTP1 and RASSF1
- “Halo phenomenon” of prostate cancer

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>p Value</td>
<td>OR</td>
<td>p Value</td>
<td>OR</td>
<td>p Value</td>
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<tr>
<td>DNA methylation</td>
<td>2.85</td>
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<td>2.53</td>
<td>0.0018</td>
<td>2.69</td>
<td>0.0002</td>
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<td>Histology:</td>
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<tr>
<td>Atypia</td>
<td>2.64</td>
<td>0.0089</td>
<td>2.37</td>
<td>0.0465</td>
<td>2.11</td>
<td>0.0531</td>
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<td>HGPIN</td>
<td>1.37</td>
<td>0.2550</td>
<td>1.11</td>
<td>0.7546</td>
<td>1.06</td>
<td>0.8434</td>
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<tr>
<td>Age</td>
<td>1.04</td>
<td>0.0319</td>
<td>1.04</td>
<td>0.0563</td>
<td>—</td>
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<tr>
<td>PSA</td>
<td>1.03</td>
<td>0.3140</td>
<td>1.04</td>
<td>0.2593</td>
<td>—</td>
<td>—</td>
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<td>Race</td>
<td>1.10</td>
<td>0.7740</td>
<td>0.96</td>
<td>0.8997</td>
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<td>—</td>
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<tr>
<td>DRE:</td>
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<td></td>
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<tr>
<td>Nodule</td>
<td>0.72</td>
<td>0.3213</td>
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<td>—</td>
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<tr>
<td>Suspicious</td>
<td>0.32</td>
<td>0.0807</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
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</table>

Partin et al, J Urol 2014
ConfirmMDx

- MATLOC and DOCUMENT studies
  - Negative predictive value = 88-90%
  - 82% likelihood of negative biopsy without the test
- Unknown effect on detection of high-grade PCa only
- Reference was result of 2nd biopsy
- Unknown effect of MRI on initial or repeat biopsy
- NCCN: an option for men considering repeat biopsy

- Cost is ~$2500 with $500 maximum out of pocket expense for patients
EXO106

A Novel Urine Exosome Gene Expression Assay to Predict High-Grade Prostate Cancer in Patients Undergoing Initial Biopsy with an Equivocal PSA


JAMA Oncology July 1, 2016
Entering the chat room of cancer cells

How cells talk, and why we have to listen
Exosomes Drive the Cellular Messaging System

Cancer Cell
Exosomes: Rich Source of Molecular Details

• Exosomes and microvesicles are secreted by virtually all cells into all biofluids, as an active process of cellular communication

• Exosomes are lipid bilayer protected vesicles, which makes them stable under varying conditions and protects their contents from degradation

• Exosomes contain RNA (mRNA, microRNA, tRNA, rRNA, lncRNA, and other RNA species), DNA and protein

Miranda K et al., Kidney International 2010; 78:191-199.
EXO106 Urine-Based Liquid Biopsy Test

3 gene signature on exosomal RNA

ERG qPCR
(ETS transcription factor, partner of TMPRSS2 fusion)

PCA3 qPCR
(LncRNA, Prostate Cancer Antigen 3)

SPDEF qPCR
(SAM pointed domain containing ETS transcription factor; androgen independent transactivator of PSA)

Multivariate Algorithm

High grade cancer (GS>6) EXO106 risk score

Intended Use:
The EXO106 risk score is used to predict the presence of high grade (GS > 7) prostate cancer for men 50 years or older with a PSA 2-10ng/mL presenting for an initial biopsy.
Discrimination for High-Grade Cancer

EXO106 + SOC:
AUC: 0.725

EXO106:
AUC: 0.711

SOC:
AUC: 0.631

PSA:
AUC: 0.545

\( \text{AUC}_{\text{EXO106+SOC}} > \text{AUC}_{\text{SOC}} \)  \( P < 0.00004 \)
Performance of the EXO106 Cut-Point to Identify High-Grade Disease in Validation Cohort

<table>
<thead>
<tr>
<th>Biopsy Result</th>
<th>Gleason≥7</th>
<th>Gleason=6</th>
<th>Total</th>
<th>Performance</th>
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</thead>
<tbody>
<tr>
<td>EXO106 &gt; cut point</td>
<td>136</td>
<td>245</td>
<td>381</td>
<td>Sensitivity % 91.89</td>
</tr>
<tr>
<td>EXO106 ≤ cut point</td>
<td>12</td>
<td>126</td>
<td>138</td>
<td>Specificity % 33.96</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>148</strong></td>
<td><strong>371</strong></td>
<td><strong>519</strong></td>
<td>PPV % 35.70</td>
</tr>
</tbody>
</table>

High Grade Biopsy Prevalence % 28.52
EXO106 Negative (%) 26.59

Majority of false negatives (9/12) were GS 3+4 with ≤ 3 positive cores

High grade disease defined as Gleason >4+3, false negative rate <5%
EXO106

• Exosomal mRNA can be isolated and analyzed using a first-catch, random urine

• The EXO106 test (combining PCA3, ERG and SPDEF) provides a high Negative Predictive Value for high-grade cancer

• Of 148 cases of Gleason 7, test only missed 3 cases of dominant pattern 4
  • False negative rate of <5%

• 2016 EXO106 now CLIA available/approved assay
# Summary

<table>
<thead>
<tr>
<th>Marker</th>
<th>Source</th>
<th>FDA</th>
<th>CLIA</th>
<th>Diagnosis</th>
<th>Prognosis</th>
<th>Cost ($)</th>
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<tbody>
<tr>
<td>PHI</td>
<td>Beckman</td>
<td>6/2012</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>70-400</td>
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<tr>
<td>PCA3</td>
<td>Hologics</td>
<td>2/2012</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>440</td>
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<td></td>
<td>Gen-probe</td>
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<tr>
<td>Exo106</td>
<td>Exosome</td>
<td>PEND</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>400-500</td>
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<tr>
<td>ConfirmDx</td>
<td>MDxHealth</td>
<td>2014</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>2400</td>
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