Update on Biomarkers for Prostate Cancer: Should I Drink the Kool-Aid?

Nathan Perlis, MD MSc
PMH Dialogues 2019 NOTL
Disclosures

• None pertaining to this talk
Overview

• Definition and aim of biomarkers
• Framework for evaluating biomarkers
• Review of main biomarkers used in localized prostate cancer
What’s a Biomarker

• WHO definition:
  – “any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease”

• In prostate cancer the term is often reserved for serum, urine or tissue tests clinically used to help with decision making or for prognostication
  – ? Re-biopsy, ? Add radiotherapy, etc.
  – Estimating survival
Biomarker = Test

• Test characteristics
  – SN, SP, PPV, NPV

• Cost

• Invasiveness

• Practicalities:
  – What does the read-out look like?
  – How will the result change your management?
• Prognostic vs Predictive
  – Marginal benefit over PSA/clinical details
• Consider specific disease state where test is intended
  –Susceptibility biomarkers
  –Biomarkers of disease risk
  –Risk stratification biomarkers
  –Biomarkers for prediction of disease response
# Table 1

Current Food and Drug Administration (FDA) or Clinical Laboratory Improvement Amendments (CLIA) approved blood-, urine-, and tissue-based biomarkers in prostate cancer.

<table>
<thead>
<tr>
<th>Biomarker Test</th>
<th>Molecular Markers</th>
<th>Available as</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum-based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate Serum Antigen (PSA)</td>
<td>PSA</td>
<td>FDA</td>
</tr>
<tr>
<td>PHI (Beckman Coulter Inc., Brea, CA, USA)</td>
<td>Total PSA, fPSA, p2PSA</td>
<td>FDA</td>
</tr>
<tr>
<td>4K (OPKO lab, Miami, FL, USA)</td>
<td>Total PSA, fPSA, intact PSA, hK2</td>
<td>CLIA-approved</td>
</tr>
<tr>
<td><strong>Urine-based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA3 (Progena) Hologic, Marlborough, MA, USA</td>
<td>PCA3</td>
<td>FDA</td>
</tr>
<tr>
<td>ExoDX Prostate (IntelliScore)</td>
<td>Exosomal RNA (PCA3, ERG)</td>
<td>CLIA-approved</td>
</tr>
<tr>
<td>Exosome Diagnostics Inc, Waltham, MA, USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MiPS (Detroit, MI, USA)</td>
<td>PCA3 and TMRSS2-ERG mRNA</td>
<td>CLIA-approved</td>
</tr>
<tr>
<td>SelectMDX (MDx Health, Irvine, CA, USA)</td>
<td>HOX6, DLX1</td>
<td>CLIA-approved</td>
</tr>
<tr>
<td><strong>Tissue-based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ConfirmMDx (MDxHealth, Irvine, CA, USA)</td>
<td>DNA hypermethylation (GSTP1, APC, RASSF1)</td>
<td>CLIA-approved</td>
</tr>
<tr>
<td>ProLaris (Myriad Genetics, Salt Lake City, UT, USA)</td>
<td>mRNA expression; 31 genes (cell cycle progression)</td>
<td>FDA</td>
</tr>
<tr>
<td>Oncotype Dx (Genomic Health, Redwood City, CA, USA)</td>
<td>mRNA expression; 17 genes</td>
<td>CLIA-approved</td>
</tr>
<tr>
<td>Decipher (GenomeDX Biosciences, San Diego, CA, USA)</td>
<td>mRNA expression; 22 genes (cell proliferation, migration, tumor motility, androgen signaling, and immune system evasion)</td>
<td>CLIA-approved</td>
</tr>
<tr>
<td>Promark (Metamark, Cambridge, MA, USA)</td>
<td>Protein biomarker test (8 proteins)</td>
<td>CLIA-approved</td>
</tr>
</tbody>
</table>
• Prognostic vs Predictive
  – Marginal benefit over PSA/clinical details
• Consider specific disease state where test is intended
  – Susceptibility biomarkers
  – Biomarkers of disease risk
  – Risk stratification biomarkers
  – Biomarkers for prediction of disease response
• Prognostic vs Predictive
  – Marginal benefit over PSA/clinical details
• Consider specific disease state where test is intended
  – Susceptibility biomarkers (SNPs, rare germline mutations)
  – Biomarkers of disease risk (MiPS, Select MDx, 4K, ExoDX)
  – Risk stratification biomarkers (4K, PHI, PCA3, Confirm MDX, Oncotype DX, Prolaris, Decipher)
  – Biomarkers for prediction of disease response (ARV7, DNA repair)
Urine and Serum tests
PCA3, 4K, Select MDX

• Predictive tests
• Typically used to consider whether or not to biopsy
• May improve long term prognostication
PCA3 Score

- Post DRE Urine
- Ratio of PCA3 : PSA mRNA

Figure 1. ROC analysis using PCA3 score or serum PSA level as diagnostic indicator and prostate biopsy as reference method.

Table 1. Sensitivity and specificity of PCA3 assay

<table>
<thead>
<tr>
<th>PCA3 Score Cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>87</td>
<td>28</td>
<td>2.5</td>
</tr>
<tr>
<td>35</td>
<td>58</td>
<td>72</td>
<td>3.6</td>
</tr>
<tr>
<td>50</td>
<td>47</td>
<td>81</td>
<td>3.7</td>
</tr>
</tbody>
</table>
## PCA3 Score

**Dynacare**

**Lab ID: 2017-264140**
University Urology Associates (UUA)/Princess Margaret Hospital

<table>
<thead>
<tr>
<th>Prescriber</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>Name:</td>
</tr>
<tr>
<td>Clinic:</td>
<td>Age:</td>
</tr>
<tr>
<td>University Urology Associates (9002)</td>
<td>77</td>
</tr>
<tr>
<td>Address:</td>
<td>Date of birth:</td>
</tr>
<tr>
<td>123 Edward Street, Suite 1401</td>
<td></td>
</tr>
<tr>
<td>Toronto, ON M5G 1E2</td>
<td>Sex:</td>
</tr>
<tr>
<td>Telephone:</td>
<td>Health Ins.</td>
</tr>
<tr>
<td>416.979.9000</td>
<td></td>
</tr>
<tr>
<td>Fax:</td>
<td></td>
</tr>
<tr>
<td>416.979.9002</td>
<td></td>
</tr>
</tbody>
</table>

### Analysis

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Result</th>
<th>Reference value</th>
<th>Unit</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCA3 (PCA3/PSA)</td>
<td>Urine</td>
<td>PCA3/PSA Ratio</td>
<td>29</td>
<td>LOW RISK</td>
</tr>
</tbody>
</table>

### Diagram

![PCA3 Score Diagram](image)

**Note:**

- **PCA3 / PSA Ratio**:PCA3 / PSA Ratio ≥ 35
- **Elevated Risk**: PCA3 / PSA Ratio ≥ 35
- **Low Risk**: PCA3 / PSA Ratio < 35
- **Indeterminate**: Insufficient quantity of PSA mRNA

**Method:**

- PCA3 mRNA copies divided by PSA mRNA copies, multiplied by 1000

This test is regarded by the scientific community as a useful adjunct in the diagnosis of prostate cancer. Decisions pertaining to patient care and treatment should not be based on a single test. Rather, decisions on care and treatment should be based on the independent medical judgment of the treating physician, taking into consideration all available information concerning the patient's condition, including other pathological tests.
In a man with a prior negative biopsy with clinical suspicion of PC (i.e. rising PSA), dual negative mpMRI and PCA3 tests is highly predictive for the absence of clinically significant prostate cancer.
Four Kallikrein (4K test)

A Multi-institutional Prospective Trial in the USA Confirms that the 4Kscore Accurately Identifies Men with High-grade Prostate Cancer


Fig. 2 – Model calibration showing predicted versus actual Gleason ≥7 cancer detected using the 4Kscore in the validation cohort.

<table>
<thead>
<tr>
<th>4Kscore cutoff</th>
<th>Biopsies performed (n)</th>
<th>Biopsies avoided, n (%)</th>
<th>Gleason ≥7 cancers, n (%)</th>
<th>Gleason score for delayed diagnosis of Gleason ≥7 cancers, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Detected</td>
<td>Delayed diagnosis</td>
</tr>
<tr>
<td>0%</td>
<td>1012</td>
<td>0 (0)</td>
<td>231 (23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>&gt; 6%</td>
<td>705</td>
<td>307 (30)</td>
<td>218 (22)</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>&gt; 9%</td>
<td>578</td>
<td>434 (43)</td>
<td>207 (20)</td>
<td>24 (2.4)</td>
</tr>
<tr>
<td>&gt; 12%</td>
<td>489</td>
<td>523 (51)</td>
<td>159 (20)</td>
<td>32 (3.2)</td>
</tr>
<tr>
<td>&gt; 15%</td>
<td>421</td>
<td>591 (58)</td>
<td>163 (18)</td>
<td>48 (4.7)</td>
</tr>
</tbody>
</table>
In a man with clinical suspicion of PC (i.e. elevated PSA) but undecided about biopsy, 4k score can help predict the likelihood of having clinically significant cancer and may inform a decision to avoid biopsy.
Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score

Leander Van Neste\textsuperscript{a,1}, Rianne J. Hendriks\textsuperscript{b,1}, Siebren Dijkstra\textsuperscript{b,1}, Geert Troostens\textsuperscript{b}, Erik B. Cornet\textsuperscript{a}, Sander A. Janssens\textsuperscript{a}, Hans de Jong\textsuperscript{b}, Daphne Hessels\textsuperscript{b}, Frank P. Smit\textsuperscript{b}, Willem J.C. Melchers\textsuperscript{2}, Gielle H.J.M. Leyten\textsuperscript{3}, Theo M. de Reijke\textsuperscript{1}, Henk Verguns\textsuperscript{b}, Paul Kijl\textsuperscript{b}, Ben C. Knipscheer\textsuperscript{1}, Christina A. Hulsbergen-van de Kaa\textsuperscript{1}, Peter F.A. Mulders\textsuperscript{1}, Inge M. van Oort\textsuperscript{b}, Wim Van Criekinge\textsuperscript{1}, Jack A. Schalken\textsuperscript{b,1}

Table 3 - Odds ratios, 95% confidence intervals, and p values for risk factors as obtained in the training cohort during development of the risk score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1, OR; CI (p)</th>
<th>Model 2, OR; CI (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOXCB and DLX1</td>
<td>1.68: 1.38–2.05 (.003)</td>
<td>1.96: 1.40–2.73 (&lt;.001)</td>
</tr>
<tr>
<td>PSA</td>
<td>5.53: 2.89–10.56 (&lt;.001)</td>
<td>3.78: 1.89–7.53 (&lt;.001)</td>
</tr>
<tr>
<td>DRE biopsy</td>
<td>0.28: 0.09–0.83 (.02)</td>
<td>0.21: 0.07–0.63 (.005)</td>
</tr>
<tr>
<td>Previous biopsy</td>
<td>5.40: 0.81–35.94 (.081)</td>
<td>3.42: 0.59–19.98 (.17)</td>
</tr>
<tr>
<td>PSA Family</td>
<td>1.76: 0.81–3.80 (.15)</td>
<td>1.56: 0.76–3.18 (.2)</td>
</tr>
<tr>
<td>Age</td>
<td>1.01: 0.97–1.05 (.7)</td>
<td>1.01: 0.97–1.06 (.5)</td>
</tr>
</tbody>
</table>

CI = confidence interval; DRE = digital rectal examination; OR = odds ratio; PSA = prostate-specific antigen; PSAD = prostate-specific antigen density.

robust predictor for the detection of high-grade PCa, as illustrated by a successful validation in this independent cohort by a direct comparison with cohort A (p = 0.3 for the difference between AUCs). In cohort B, model 2 reached an
In a man with clinical suspicion of PC (i.e. elevated PSA) but undecided about biopsy, Select MDX score can help predict the likelihood of having clinically significant cancer and may inform a decision to avoid biopsy.
In a man where suspicion of GI7 PC is borderline (i.e. mildly elevated PSA) but undecided about biopsy, Select MDX score can may inform a decision to avoid or proceed with biopsy.
Tissue based tests
Decipher, Prolaris, Oncotype DX

• Uses biopsy or RP specimen tissue
• Predictive tests
  – Genomic classifiers
• Typically used to consider whether or not to treat
  – Primary or adjuvant
Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease


**Fig 1.** Cumulative incidence of metastasis over time stratified by genomic risk groups (also referred to as Decipher risk categories): low, intermediate, and high. RP: radical prostatectomy.

**Fig 2.** Correlation of the genomic-risk score (Decipher Score) to the following clinicopathologic variables: (A) preoperative prostate-specific antigen (PSA); (B) radical prostatectomy (RP) Gleason score; (C) surgical margins; (D) extraprostatic extension; (E) seminal vesicle invasion; and (F) lymph node invasion.
In a man with localized prostate cancer Decipher can be used to

Predict metastasis
Better risk stratify patients
Triage adjuvant or salvage therapy (NCCN guideline)
Decipher Test Impacts Decision Making Among Patients Considering Adjuvant and Salvage Treatment After Radical Prostatectomy: Interim Results From the Multicenter Prospective PRO-IMPACT Study

John L. Gore, MD, MS; Marguerite du Plessis, BSc; María Santiago-Jiménez, MS; Khia Yousef, MS; Derby J. S. Thompson, PhD; Lawrence Kersh, MD; Brian R. Lane, MD, PhD; Michael Feinna, MD; David Y. J. Chen, MD; Mark Bandyk, MD; Fernando J. Blanco Jr., MD; Gordon Brown, DO; William Clark, MD; Adam S. Kibel, MD; Hyung L. Kim, MD; William Lowrance, MD, MPH; Munyesan Manoharan, MD; Paul Maroni, MD; Scott Perrapato, DO; Paul Sieber, MD; Edouard J. Tabuski, MD; Robert Waterhouse, MD; Eil Daviddson, PhD; Yair Lotan, MD; and Daniel W. Lin, MD

Figure 2. (A) Changes in treatment recommendation by Decipher risk category in the adjuvant radiotherapy arm. (B) Changes in treatment recommendation by Decipher risk category in the salvage radiotherapy arm. ADT indicates androgen deprivation therapy; Int, intermediate; RT, radiotherapy.
Prolaris
Oncotype DX

Genomic Prostate Score® (GPS®) Report

**PATIENT-LAST-NAME, FIRST-NAME I.**

Date of Birth: 18-Jan-1961  
Gender: Male  
Report Number: 0R000123456-01  
Report Date: 20-May-2019

**Ordering Physician:** Dr. First-Name I. Ordering-Physician-Last-Name

**GPS + NCCN®: LOW RISK**


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The combination of GPS and clinical features predicts that this patient's risk is consistent with NCCN Low Risk disease. In a clinical validation study including patients with NCCN Low Risk (low and intermediate) risk, no patient with a GPS score 0-10 had metastasis or died from prostate cancer within 10 years.  

**Metastasis Within 10 Years:** 4%  
(95% Confidence Interval: 0-16%)

**Prostate Cancer Death Within 10 Years:** 1%  
(95% Confidence Interval: 0-16%)

**Adverse Pathology:** 31%  
(95% Confidence Interval: 23%-41%)

**NCCN Risk Group:** Intermediate

**Physician-Provided Information:**

- ** Gleason Score:** 3+3
- **PSA (ng/ml):** 12.0
- **MRI Density Inhomogeneity:** 0.21
- **C1 Stage:** T1c
- **Max. % of tumor involvement in any core:** ≤ 50%
- **Number of cores positive:** 11
- **Number of cores collected:** 14

**NCCN Guidelines** lead to a subset of favorable intermediate-risk prostate patients: 1. Gleason grade 3+3 (Gleason score 2+4+4+4), 2. percentage of prostate core Gleason, and no more than one NCCN intermediate-risk factor.

- **GPS Distribution in NCCN Intermediate Risk:**
  - More Favorable: 16%  
  - Less Favorable: 31%

- **Pathology Endpoints**
  - **High-Grade Disease:** 15%  
  - **Non-Organ-Confined Disease:** 16%

This patient has a GPS result that is lower than the average GPS result for NCCN Intermediate Risk.

The Oncotype DX Genomic Prostate Score GPS test is a continuous scale (0-100) that quantifies expression of 17 genes in tumor tissue as assessed by RT-PCR. The GPS test has been validated in three prospectively designed studies (N=1056) of biopsy tissue from patients with localized prostate cancer. Adverse pathology refers to the finding of an aggressive tumor (high grade) or cancer spread outside of the prostate (non-organ-confined). Tumors with a low risk of adverse pathology are less likely to be aggressive and spread.

**Laboratory Director:** Patrick Joseph, MD

This test was developed and its performance characteristics determined by Genomic Health, Inc. It has not been cleared or approved by the FDA, nor is it currently required to be. The laboratory is regulated under CAP as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or research.
Summary

• “Biomarkers” are tests with fancy names
  – If no marginal benefit over standard nomogram - don’t use
• Serum and urine tests can help decide on whether or not to biopsy (4K, PCA3, Select MDX)
• Tissue tests (Decipher, OncotypeDX, Prolaris) can predict survival and adverse findings on RP and used to decide on adjuvant radiotherapy
• Expensive
• No trials yet to prospectively test whether altering treatment based on genomic classifier improves outcome
Will you drink the Kool-Aid?
Update on Biomarkers for Prostate Cancer: Should I Drink the Kool-Aid?

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