How will new biomarkers change prostate cancer management

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Disclosures

• Consulting relationships with:
  • Astellas
  • Dendreon
  • Myriad

• Institutional research support:
  • GenomeDx
  • Genomic Health
  • Myriad
Prostate cancer 2016: Decision, decisions...

- Draw PSA?
  - SNPs?
  - PCA3
  - phi
  - 4K score
  - SelectMDx
  - ExoDx

- 1st biopsy?
  - ConfirmMDx
  - PCA3
  - phi
  - 4K panel
  - OncoType
  - Prolaris
  - Decipher
  - Promark

- 2nd biopsy?
  - OncoType
  - Prolaris
  - Decipher
  - Promark

- Pre-treatment
  - Decipher
  - Prolaris
  - OncoType

- Post-op treatment?
  - Decipher
  - Prolaris
  - OncoType

- mpMRI
  - PSMA-PET/CT

- Advanced disease
  - ARv7?
Pre-diagnosis principles

1. Any candidate marker has to improve on an existing multivariable gold standard (not just PSA).
   Risk calculators: e.g. PCPT, ERSPC, Sunnybrook

2. High-quality methodology is absolutely critical, especially for retrospective studies.
   • **REporting of tumor MARKer (REMARK)** guidelines – McShane et al. JCO 2005; 23:9067
   • Prospective-specimen collection, **Retrospective Blinded Evaluation (PROBE)** - Pepe et al. JNCI 2008; 100:1432

3. The goal is *not* identification of prostate cancer. The goal is identification of **potentially lethal** prostate cancer.
Should we consider pre-PSA testing in the population?

Evaluation of Multiple Risk-Associated Single Nucleotide Polymorphisms Versus Prostate-Specific Antigen at Baseline to Predict Prostate Cancer in Unscreened Men

Robert J. Klein a,*, Christer Hallden b,†, Amit Gupta c,†, Caroline J. Savage d, Anders Dahlin e, Anders Bjartell f, Jonas Manjer g, Peter T. Scardino c, David Ulmert c f, Peter Wallström h, Andrew J. Vickers d, Hans Lilja b c i

<table>
<thead>
<tr>
<th>Any prostate cancer</th>
<th>Aggressive or advanced prostate cancer (clinical stage ≥T3, evidence of metastasis, WHO grade 3, or Gleason stage ≥8 at diagnosis)</th>
<th>Advanced prostate cancer (clinical stage ≥T3 or evidence of metastasis at diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA alone</td>
<td>0.792 (0.774–0.810)</td>
<td>0.823 (0.792–0.855)</td>
</tr>
<tr>
<td>PSA plus SNPs</td>
<td>0.791 (0.773–0.809)</td>
<td>0.811 (0.777–0.844)</td>
</tr>
<tr>
<td>SNPs alone</td>
<td>0.571 (0.548–0.594)</td>
<td>0.498 (0.455–0.541)</td>
</tr>
</tbody>
</table>

WHO = World Health Organization; SNP = single nucleotide polymorphism.
† All estimates have been corrected for overfit using 10-fold repeated cross-validation and are reported as area under the curve (95% confidence interval).
Tests to consider before a first biopsy

- PCA3
- 4K
- phi
- SelectMDx
- ExoDx
- mpMRI

Individualized Risk Assessment of Prostate Cancer
PCPTRC 2.0

Based on the provided risk factors a prostate biopsy performed would have a:

- 12% chance of high-grade prostate cancer,
- 18% chance of low-grade cancer,
- 70% chance that the biopsy is negative for cancer.

About 2 to 4% of men undergoing biopsy will have an infection that may require hospitalization.

Please consult your physician concerning these results. Click here to watch a video overview of these results.
Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer

Tobias Nordström\textsuperscript{a,b,*}, Andrew Vickers\textsuperscript{c}, Melissa Assel\textsuperscript{c}, Hans Lilja\textsuperscript{d,e,f}, Henrik Grönberg\textsuperscript{b}, Martin Eklund\textsuperscript{b,g}

\textbf{phi:} PSA, fPSA, -2proPSA  
\textbf{4K:} PSA, fPSA, iPSA, HK2

\textit{Conclusions:} The four-kallikrein panel and PHI similarly improved discrimination when predicting PCa and high-grade PCa. Both are simple blood tests that can reduce the number of unnecessary biopsies compared with screening with total PSA, representing an important new option to reduce harm.
4K and phi

Any cancer

High-grade cancer

SelectMDx

- Urinary assay for *HOXC6* and *DLX1* mRNA transcripts
- Validated in 2 multicenter cohorts across 6 centers in the Netherlands (N=519, N=386), mixed de novo and repeat biopsy

ExoDX

• Assessment of urinary exosomal RNA (PCA3, TMPRSS2:ERG, SPDEF as control) without prior DRE

• N=255 training, N=519 validation

McKiernan et al. JAMA Oncol 2016; 2:882
Tests to consider before a repeat biopsy

PCA3
4K
phi
ConfirmMDx
mpMRI

Routinely include anterior cores

ConfirmMDx

- Biopsy
- Cancer
- Field Effect

Methylation of
- GSTP1
- APC
- RASSF1
ConfirmMDx Risk Profile Score

Outperforms traditional score methods like PSA and Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator 2.0 (PCPTRC2)

NPV for high-grade disease: 96%

Van Neste et al. Prostate 2016; 78:1078
Post-diagnosis: similar principles

A putative biomarker must improve on an existing, *multivariable* clinical model, ideally a previously validated one.

Nomograms
CAPRA / CAPRA-S

*Not* just Gleason score alone or the D’Amico / NCCN risk groups
The bar is high for improved accuracy

C-index = 0.79
Prolaris (Myriad Genetics)

Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study


31 cell cycle progression (CCP) genes, normalized to 15 housekeeper genes

Score is expressed as average centered expression of CCP genes relative to housekeeper genes; negative scores = less active CCP, positive scores = more active CCP

Predicts mortality from biopsy

Biomarkers vs. clinical parameters

Cooperberg et al, JCO 31:1428, 2013
CCP score stratifies outcomes

Cooperberg et al, JCO 31:1428, 2013
Cox model of PGP

| CCP score | Univariate | | | | Adjusted model 1 | | | | | | Adjusted model 2 | | |
|-----------|------------|------------|------------|---|------------|---|------------|---|------------|---|------------|---|
|           | HR  | p    | 95% CI | HR  | p    | 95% CI | HR  | p    | 95% CI |
| ≤-1       | ref  |       |        |     |       |        |     |       |        |     |       |        |
| >-1 – 0   | 3.5  | 0.08  | 0.9 – 14.6 | 3.3 | 0.10  | 0.8 – 13.6 | 2.9 | 0.15  | 0.7 – 12.0 |
| >0 – 1    | 6.8  | 0.009 | 1.6 – 28.3 | 5.1 | 0.03  | 1.2 – 21.4 | 4.7 | 0.04  | 1.1 – 19.8 |
| >1        | 14.9 | 0.001 | 3.1 – 70.3 | 9.4 | 0.005 | 2.0 – 44.7 | 12.7 | 0.002 | 2.5 – 63.3 |

Model 1 = adjusted by CAPRA-S

Model 2 = adjusted by individual clinical variables

C-index 0.73 for CAPRA-S vs. 0.77 for combined model
10-year PGP predictions

Cooperberg et al, JCO 31:1428, 2013
**Onco*type* DX GPS (Genomic Health)**

- Quantitative 17-gene RT-PCR assay on manually microdissected tumor tissue from needle biopsy
- Genes and biological pathways predictive of multiple endpoints, with emphasis on clinical recurrence
- Optimized for very small tissue input: six 5 micron sections of single needle biopsy block with as little as 1 mm tumor length

<table>
<thead>
<tr>
<th>Cellular Organization</th>
<th>Androgen Signaling</th>
<th>Stromal Response</th>
<th>Proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLNC, GSN, GSTM2, TPM2</td>
<td>AZGP1, FAM13C, KLK2, SRD5A2</td>
<td>BGN, COL1A1, SFRP4</td>
<td>TPX2</td>
</tr>
</tbody>
</table>

**GPS** = 0.735*Stromal Response group - 0.352*Androgen Signaling group + 0.095*Proliferation group - 0.368*Cellular Organization group

Scaled between 0 and 100
Weak correlation between CAPRA and GPS

## Multivariable Performance of GPS

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GPS (per 20 units)</td>
<td>1.85</td>
<td>(1.23, 2.81)</td>
<td>0.003</td>
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<tr>
<td></td>
<td>Age (continuous)</td>
<td>1.05</td>
<td>(1.01, 1.09)</td>
<td>0.004</td>
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<tr>
<td></td>
<td>PSA (continuous)</td>
<td>1.11</td>
<td>(1.04, 1.18)</td>
<td>0.002</td>
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<tr>
<td></td>
<td>Clinical Stage T2 vs. T1</td>
<td>1.57</td>
<td>(0.98, 2.51)</td>
<td>0.059</td>
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<tr>
<td></td>
<td>Biopsy Gleason Score (7 v. 6)</td>
<td>1.70</td>
<td>(1.00, 2.88)</td>
<td>0.050</td>
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<tr>
<td>2</td>
<td>GPS (per 20 units)</td>
<td>2.13</td>
<td>(1.44, 3.16)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>CAPRA</td>
<td>1.58</td>
<td>(1.24, 2.02)</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Adding GPS to CAPRA: predicting pathology

- CAPRA 0 = 86%
- CAPRA 1 = 78%
- CAPRA 2 = 67%
- CAPRA 3 = 55%
- CAPRA 4 = 43%

49% of pts have ≥5% change in predicted risk
26% to more favorable
23% to less favorable

Additional validation studies

Prolaris

- Predicting BCR and mets following surgery based on biopsy (Bishoff J Urol 2014)
- Predicting BCR after EBRT (Freedland IJROBP 2013)
- Prolaris as outcome in fish oil diet study (Galet, Cancer Prev Res 2014).

OncoType GPS

- Prediction of adverse pathology and BCR following prostatectomy in CPDR cohort (Cullen Eur Urol 2014)
22-gene genomic classifier, with genes chosen purely by statistical selection to predict metastasis among high-risk RP patients, no pathway analysis (includes non-coding genes, 3 unknowns)

Rather than RT-PCR on established gene set, clinical assay is run using Affymetrix Human Exon 1.0ST GeneChip (1.4M probe sets interrogating 5.5M features of whole exome)

Decipher score is calculated, but a large trove of data is kept in the databank for ongoing / future discovery

Erho et al., PLoS ONE 8:e66855, 2013
Genomic reclassification

PORTOS score for post-op radiation

High PORTOS

Low PORTOS

Zhao et al. Lancet Oncol 2016 epub
Decipher GRID

**GENOMIC PROFILE SUMMARY**

- Molecular subtype signatures (P.2)
  - Neuroendocrine/small cell
  - Adenocarcinoma
  - Luminal
  - Basal
  - ERG
  - ETS
  - SPINK1
  - TripleNeg

**PREDICTIVE (P.3)**
- ADT response: 78%
- Radiation response: 54%
- Docetaxel sensitivity: 27%
- Dasatinib sensitivity: 67%

**PROGNOSTIC (P.4)**
- Risk of metastasis (average of 18 signatures)*: 19%

**TUMOR GRADE/STAGE (P.5)**
- Genomic Gleason grade: 8

**MOLECULAR PATHWAYS (P.5)**
- Tumor cell proliferation (average of 3 signatures)*: 24%
- AR signaling activity (average of 2 signatures)*: 61%

**SELECT RNA MARKERS - TOP OUTLIERS (P.6)**
- RNA marker most over-expressed: VEGFR2
- RNA marker most under-expressed: EZH2

- PERCENTILE RANK
  - VEGFR2: 100%
  - EZH2: 5%
“Next generation” liquid biopsy

Coming soon:

Plasma miRNA
CTC enumeration/sequencing
Cell-free DNA

Stay tuned...!
Conclusions and future questions

Emerging biomarkers offer improved *prognostic* information compared to clinical parameters alone.

How to (really) use these tests in clinical practice is mostly unclear.

Can we do a better job *customizing* active surveillance (Can some men be stratified to watchful waiting? Can a subset be “undiagnosed”?)

Are these tests cost-effective?

Molecular subtyping is finally in sight for prostate cancer.

We are barely even at the “end of the beginning”
Thank you — UCSF Urologic Oncology

<table>
<thead>
<tr>
<th>Peter Carroll</th>
<th>Felix Feng</th>
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<tr>
<td>June Chan</td>
<td>Janet Cowan</td>
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<td>Stacey Kenfield</td>
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Questions?