Genomic Markers in Prostate Cancer Decision Making

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Director of Prostate Cancer Department, Brazilian Society of Urology
Pre-treatment
Risk stratification
biomarkers
PREGNANCY TESTS

MAYBE BABIES
Oncotype DX

GPS Validation:
Prediction of Adverse Pathology

Prostate Cancer Technical Feasibility

Prostatectomy Study (Cleveland Clinic)
Two tumor foci per patient (n=441)
Clinical Recurrence, PCSS, Adverse Pathology at RP

Biopsy Study (Cleveland Clinic)
Biopsy specimens (n=167)
Adverse Pathology at RP

Assay Finalization and Analytical Validation
17-Gene GPS Assay

UCSF Clinical Validation Study
Biopsy Specimens (n=395)
Adverse Pathology at RP
GPS Prediction of Grade And Stage

- Binary univariate logistic regression
- 20 GPS units analogous to comparison of top vs. bottom quartiles of patients

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>LR Chi-Square</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prediction of High Grade Disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPS per 20 units</td>
<td>2.48</td>
<td>(1.60, 3.85)</td>
<td>16.78</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Prediction of pT3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPS per 20 units</td>
<td>2.20</td>
<td>(1.46, 3.31)</td>
<td>14.44</td>
<td>&lt;0.001</td>
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</tbody>
</table>
Oncotype

GPS + NCCN<sup>81</sup>: Low Risk

The combination of GPS and clinical features predicts that this patient’s risk is consistent with NCCN Low Risk disease.<sup>3</sup>

<table>
<thead>
<tr>
<th>Clinical Interpretation</th>
<th>Clinical Endpoints&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Individualized Risk (95% Confidence Interval [CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer Death Within 10 Years</td>
<td>&lt;1% (95% CI: &lt;1% - &lt;1%)</td>
<td>100%</td>
</tr>
<tr>
<td>Metastasis Within 10 Years&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1% (95% CI: &lt;1% - 6%)</td>
<td>100%</td>
</tr>
<tr>
<td>Adverse Pathology (Gleason ≥4+3 and/or pT3+)</td>
<td>22% (95% CI: 17% - 28%)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Pathology Endpoints** | Individualized Risk (95% Confidence Interval [CI])

| High-Grade Disease (Gleason ≥4+3) | 13% (95% CI: 10% - 17%) |
| Non-Organ-Confined Disease (pT3+) | 15% (95% CI: 12% - 16%) |
Incorporation of the Genomic Prostate Score (GPS) as part of the decision algorithm for patients with very low risk and low-risk cancer led to substantial increase in uptake of AS and substantial cost savings.
The Prolaris Assay

- Material = RNA expression

- 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

Prolaris
CCP and CAPRA combined.

Cooperberg et al. JCO 31:1428, 2013
Impact of the CCP test on physician and patient treatment selection for localized prostate cancer

Neal D. Shore, Naveen Kella, Brian Moran, Judd Boczko, Fernando J. Bianco, E. David Crawford, Thaylon Davis, Kirstin M. Roundy, Kristen Rushton, Charles Grier, Rajesh Kaldate, Michael K. Brawer, Mark L. Gonzalgo

The CCP test has a significant impact in assisting physicians and patients reach personalized treatment decisions.

mean number of treatments per patient decreasing from 1.72 pre-CCP test to 1.16

The CCP test has a significant impact in assisting physicians and patients reach personalized treatment decisions.
Decipher: Risk of Metastases post RP

- Decipher is a 22-gene genomic classifier, with genes chosen purely by statistical selection to predict metastasis among high-risk RP patients at Mayo, no pathway analysis (includes non-coding genes, 3 unknowns)
- Rather than RT-PCR on established gene set, clinical assay is run using Affy Human Exon 1.0ST GeneChip (1.4M probe sets interrogating 5.5M features of whole exome)
- Decipher score is calculated, but an enormous trove of data is kept in the databank for ongoing / future discovery

Erho et al., PLoS ONE 8:e66855, 2013
Decipher
Decipher

Capra Score and GC are Correlated
Decipher

**CLINICAL DETAILS**
- PSA, Most Recent (ng/mL): **4.1**
- Specimen Type: **Needle Biopsy**
- NCCN Risk Category: **Low Risk**
- # of Positive Cores: **8 (8 of 32 Cores)**
- Gleason Score: **3+3**
- Clinical Stage: **T2a**

**YOUR DECIPHER RESULT: GENOMIC HIGH RISK**

<table>
<thead>
<tr>
<th>DECIPHER SCORE: 0.99</th>
</tr>
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<tbody>
<tr>
<td><strong>High Grade Disease (primary Gleason grade 4 or 5)</strong></td>
</tr>
<tr>
<td>5-Year Metastasis</td>
</tr>
<tr>
<td>10-Year Prostate Cancer Specific Mortality</td>
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</tbody>
</table>

**INTERPRETATION**

Clinical studies have shown that men with a Decipher high risk have an unfavorable prognosis. These men may not be suitable candidates for active surveillance and may benefit from intensification with multi-modal therapy.13
## Pre-treatment Risk stratification biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Company/Institute</th>
<th>Test Type</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decipher</td>
<td>GenomeDX Biosciences</td>
<td>Radical prostatectomy</td>
<td>22</td>
<td>Decipher scores, in addition to clinical variables, predict 10-yr distant metastasis after surgery (AUC = 0.81). GC (alone or plus CAPRA score) has a higher ability to predict the occurrence of metastases (AUC = 0.83–85).</td>
</tr>
<tr>
<td>Oncotype DX</td>
<td>Genomic Health Inc.</td>
<td>Prostate biopsy</td>
<td>17</td>
<td>GPS combined with clinical parameters (age, PSA, clinical stage, and biopsy GS) or with the CAPRA score is a predictor of high-grade (primary GS of 4 or any pattern of 5) or high-stage disease (pT3 or higher), and BCR.</td>
</tr>
<tr>
<td>Prolaris</td>
<td>Myriad Genetics</td>
<td>Prostate biopsy</td>
<td>31</td>
<td>CCP score is an independent predictor of PCa death, BCR, and metastasis after radical prostatectomy and radiation therapy.</td>
</tr>
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</table>

A favorable prediction for each was defined as follows:

- Decipher and Prolaris: likelihood of 10 year PCM= 3%;
- Oncotype DX: >70% likelihood of organ confined, Grade Group 1 or 2

Decipher – Prolaris agreement = 67%
Prolaris – Oncotype =75%
Decipher - Oncotype = 50%

Decipher – NCCN= 60%
Prolaris – NCCN =75%
Oncotype – NCCN = 50%

Notable differences exist in favorable prognostic outcomes obtained from Oncotype Dx, Prolaris, and Decipher. **Prolaris is most apt to confirm NCCN recommendation while Oncotype DX is more likely to go against it**
Biological markers appear promising to guide care of men with AS. However, they have not yet been prospectively robustly tested in the AS setting. Therefore, while waiting for further data and even though some men may benefit for assessment of these biomarkers, their use cannot be currently routinely recommended in AS.
Post-treatment
Risk stratification
biomarkers
Pre-primary treatment

- OncotypeDx genomic prostate score
- Prolaris
- Decipher

Post-primary treatment

- Decipher
- Prolaris
- OncotypeDx GPS
In patients treated with post-RP RT, GC is prognostic for the development of clinical metastasis beyond routine clinical and pathologic features. Pts with low GC scores are best treated with salvage RT, whereas those with high GC scores benefit from adjuvant therapy.
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Knowledge of Decipher test results was associated with treatment decision making and improved decisional effectiveness among men with PCa who were considering ART and SRT.
Prostate Cancer Biomarkers

DECIPHER POST-OPERATIVE REPORT

PATIENT DETAILS
Patient Name: 
Medical Record Number: 
Date of Birth: 
Date of Prostatectomy: 
Patology Laboratory: 
Pathologist: 
Address:

ORDER INFORMATION
Order Date: 
Specimen Received Date: 
GenomeDx Accession ID: 
Specimen ID: 
Ordering Physician: 
Clinic/Hospital Name: 
Clinic/Hospital Address: 
Additional Physician:

CLINICAL DETAILS
PSA, most recent (ng/mL): **4.9**
Gleason Score: **4+3**
Specimen Type:
- SM+ 
- EPE 
- SVI 
- LNI 
- BCR 
- Tertiary Gleason 5

YOUR DECIPHER RESULT - GENOMIC LOW RISK

<table>
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<tr>
<th>DECIPHER SCORE 0.3</th>
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<td><strong>Risk - Percent Likelihood</strong></td>
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INTERPRETATION

Clinical studies concluded that Decipher low risk results in men with adverse pathology have good prognosis overall and may be optimally managed with observation after surgery. Upon PSA rise, these patients may be treated with delayed radiotherapy without concurrent hormone therapy.

Relevant findings from published clinical studies: Patients with Decipher low risk had >97% 5-year metastasis free survival and >94.7% 10-year cause specific survival. For these patients there were no significant differences in metastasis free survival with adjuvant, early or late salvage postoperative radiotherapy treatment.

In patients with PSA rise or biochemical recurrence after surgery that received salvage radiotherapy, >97% 5-year metastasis free survival was observed with or
Genomics in Michigan Impacting Observation or Radiation (G-MINOR)

Number of participants that receive adjuvant therapy (radiation and/or hormone therapy)
Genomic make-up varies widely among CaP foci, so care should be taken when making treatment decisions based on a single biopsy or index lesions.