Point-Counterpoint: There Is A Role for Currently Available Biomarkers/Genomics in the Risk Stratification of Prostate Cancer

PRO:

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Views represent my own and not that of the DoD

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No financial disclosures
Risk Stratification

Why does it matter?

• **AS vs treatment**
• Going wide
• Margining in EBRT planning
• Extent of node dissection
• Neoadjuvant HT
• Adjuvant EBRT
What we have without biomarkers?

- We will leave PSA in the “without biomarkers” category
- Exam, Gleason score, % positive
- NCCN, MSK nomogram, CAPRA
# NCCN Guidelines Version 4.2018
## Prostate Cancer

### RISK STRATIFICATION AND STAGING WORKUP

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Clinical/pathologic features</th>
<th>Imaging(^{ij})</th>
<th>Molecular testing of tumor</th>
<th>Germline testing</th>
</tr>
</thead>
</table>
| Low\(^{d}\)              | • T1-T2a AND  
• Gleason score ≤6/grade group 1 AND  
• PSA <10 ng/mL                                                                                   | Not indicated                          | Consider if life expectancy ≥10y\(^{l}\)           | Consider if strong family history\(^{c}\) |
| Favorable intermediate\(^{g}\) | • T2b-T2c OR  
• Gleason score 3+4=7/grade group 2 OR  
• PSA 10–20 ng/mL  
• Percentage of positive biopsy cores <50%                                                  | • Bone imaging\(^{b}\): not recommended for staging  
• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement | Consider if life expectancy ≥10y\(^{l}\)           | Consider if strong family history\(^{c}\) |
Oncotype DX
Prolaris
Promark
Decipher
17-Gene Genomic Prostate Score (GPS)

- **Genes Associated with Worse Outcome**
  - Stromal Response
    - BGN
    - COL1A1
    - SFRP4
  - Proliferation
    - TPX2

- **Genes Associated with Better Outcome**
  - Androgen Signaling
    - AZGP1
    - FAM13C
    - KLK2
    - SRD5A2
  - Cellular Organization
    - FLNC
    - GSN
    - GSTM2
    - TPM2

- **Reference Genes**
  - ARF1
  - ATP5E
  - CLTC
  - GPS1
  - PGK1

GPS (scaled 0-100) =
{Stromal Response Group} + {Proliferation} - {Androgen Signaling Group} - {Cellular Organization Group}
Aim:
To evaluate the association of GPS with tumor aggressiveness in the CPDR cohort, as measured by:

- Biochemical recurrence (BCR) after radical prostatectomy (RP)
- Adverse pathology (AP) at surgery
Study Design and Methods

- 402 men treated with RP between 1990-2011 at two US Military Treatment Facilities:
  - Madigan Army Medical Center, 254 subjects
  - Walter Reed National Military Medical Center, 148 subjects
- Patients with NCCN very low, low, and intermediate risk prostate cancer were included
- GPS (100-unit scale) was assessed by RT-PCR of mRNA from archival fixed paraffin-embedded needle biopsy tumor tissue
- All biopsy and RP specimens were centrally reviewed by a single expert uropathologist (IAS) following ISUP 2005 criteria
Study Design and Methods

- Clinical events
  - 62 BCR events after RP
    - defined as either two successive PSA level $> 0.2$ ng/mL ($n=57$), or the initiation of salvage therapy after a PSA rise ($n=5$)
  - 163 AP events at RP
    - defined as either high-grade disease (primary Gleason pattern 4 or any pattern 5), and/or non-organ confined disease (pT3)
- Cox proportional hazard models were used for time to BCR
- Logistic regression models were used for analysis of AP
A Wide Distribution of GPS Values Within Different Clinical Sub-groups
GPS Was Associated with BCR in Univariable (N=402) and Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPS per 20 Units</td>
<td>2.93</td>
<td>(2.03-4.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GPS per 20 Units</td>
<td>2.73</td>
<td>(1.84-3.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NCCN Risk Group*: Low vs Very Low</td>
<td>1.88</td>
<td>(0.56-11.71)</td>
<td>0.349</td>
</tr>
<tr>
<td>Int. vs Very Low</td>
<td>2.17</td>
<td>(0.63-13.72)</td>
<td>0.249</td>
</tr>
</tbody>
</table>

* n = 392 (NCCN risk group was missing for 10 patients)

In multivariable analysis, GPS remained as the only significant predictor of time to BCR.
GPS was significantly associated with AP (p< 0.001) after adjustment for the significant clinical and pathology factors from univariate analysis.

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<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPS per 20 Units</td>
<td>3.23</td>
<td>(2.14-4.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GPS per 20 Units*</td>
<td>2.74</td>
<td>(1.77-4.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at Diagnosis (Years)</td>
<td>1.06</td>
<td>(1.02-1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NCCN Risk Group: Low vs Very Low</td>
<td>3.44</td>
<td>(1.43-9.65)</td>
<td>0.0047</td>
</tr>
<tr>
<td>Int. vs Very Low</td>
<td>5.20</td>
<td>(2.05-15.18)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*n=372 (NCCN risk group was missing for 10 patients)
ROC’s With and Without GPS Results

Biochemical Recurrence

Adverse Pathology
Meta with UCSF
Objectives

1) To determine if GPS added predictive value to three widely used clinical risk assessment tools (CAPRA score, NCCN risk group, and AUA/EAU risk group)

2) To provide a more accurate estimate of the proportion of patients who have a very low risk of harboring AP
Results

Evaluable population in UCSF Study  
N=395

6 (2%) excluded for pT2+

Evaluable population in CPDR Study  
N=402

13 (3%) excluded for central biopsy GS 4+3
7 (2%) excluded for unevaluable RP slides
39 (10%) excluded for pT2+

Eligible for meta-analysis for AP endpoint  
N=389

Eligible for meta-analysis for AP endpoint  
N=343

Included in meta-analysis  
N=732
GPS Adds Predictive Value for the Likelihood of Favorable Pathology to Different Clinical Risk Assessment Tools

Likelihood ratio tests showed that GPS adds statistically significant predictive value for the LFP to each clinical risk tool in each study individually (both \( p \leq 0.002 \)) and in the meta-analysis (\( p < 0.001 \)).
Risk Profiles for GPS and CAPRA Score
Risk Profiles for GPS and NCCN Risk Group

Graph showing the probability of favorable pathology against GPS values for different risk groups:
- NCCN Very Low
- NCCN Low
- NCCN Intermediate

Legend:
- Meta-Analysis Model

Y-axis: Probability of Favorable Pathology
X-axis: GPS
Risk Profiles for GPS and AUA/EAU Risk Group

GPS further discriminated patients’ LFP, yielding a wide range of LFP within each risk group. Combining GPS with CAPRA score provided the most individualized LFP estimates and the widest range of LFP among individual patients.
Area Under the Curve (AUC) of Receiver Operating Characteristics (ROC) from Patient-Specific Meta-Analysis.

Using GPS together with each clinical risk assessment tool significantly improved the AUC compared with the clinical risk assessment tool alone (p<0.001)
Badani Clinical Utility Study
Oncotype DX
Methods

• Patients with NCCN very-low– to low-intermediate–risk prostate cancer, defined as Gleason score 6 or low-volume Gleason pattern 3+4 and cT1c–cT2c and PSA ≤20, ≥50 years old with a >10-year life expectancy were eligible

• Conducted at three sites (Delaware Valley Urology, Orange County Urology, and New York-Presbyterian Hospital/ Columbia University)

• Urologists indicated treatment recommendations on pre- and post-assay questionnaires
Badani Clinical Utility Study
Oncotype DX
Conclusions

• Incorporation of GPS resulted in a treatment recommendation change in 41 of 158 (26%) of all patients
  – There was a 24% relative increase in recommendations for AS (41% to 51%)
    • Of 67 patients initially recommended for RP with standard lymph node dissection, 17 (30%) were recommended AS
  – Of 64% of patients initially recommended AS 6 (9%) were recommended RP after GPS
  – All changes were directionally consistent with GPS (ie, higher GPS led to more aggressive management recommendations and vice versa)

• These data suggest that the GPS can influence treatment recommendations, particularly in men with NCCN low-risk disease

• GPS provides substantial utility and increased confidence in treatment recommendations

• This may lead to increased acceptance and compliance with the urologist’s treatment recommendation

Urol Pract. 2015
Dall’Era Clinical Utility
Oncotype DX
Study Design

Design
• Retrospective study to assess the impact of Oncotype DX® GPS on treatment recommendations and treatment implemented
• All physicians were in community-based practices (93% LUGPA)

Study Population
• Eligible investigators identified from the commercial database provided chart-based review for two groups of similar patients:
  – Group 1 (baseline): treated prior to Oncotype DX becoming commercially available
  – Group 2 (tested): treated after Oncotype DX GPS became commercially available
• N = 211
  – 124 GPS patients
  – 87 Baseline patients

Dall’Era et al. *Urol Pract.* 2015
Treatment Recommendations (n=174)

- Active Surveillance (AS) was recommended for a greater proportion of patients when Oncotype DX GPS was included in the decision-making process
  - 22% relative increase in patients recommended AS
  - 50% of patients were recommended without GPS
  - 61% of patients were recommended with GPS
  - Incorporating GPS resulted in increased recommendations for AS across all risk groups studied

_Urol Pract._ 2015.
Dall’Era Clinical Utility
Oncotype DX
Conclusions

• Recommendations of AS were directionally consistent with GPS
  — Largest absolute increases in AS were observed in NCCN very-low and low patients
  — Increased use of AS as likelihood of favorable pathology increases

• AS was recommended more frequently when the Oncotype DX was included in treatment planning discussion

• When the GPS was integrated, physicians saw a dramatic increase in patients accepting AS
  — Even in practices with high baseline AS rates (43%), the GPS results made a significant impact (67%) on initial treatment pursued

_Urol Pract._
2015.
Prolaris combines RNA expression of cell cycle progression (CCP) genes with standard clinicopathologic parameters.

- 31 genes across multiple cell cycle progression pathways
- 15 housekeeper genes
- CCP genes encode products that are required during cell cycle progression, and they need to be regulated at the level of RNA expression (Whitfield et al. Mol. Biol. Cell 2002)

Prolaris Measures Cellular Proliferation
Prolaris has proven clinical utility

- In two clinical utility studies Prolaris results lead to change in management in up to 65% of patients
- Prolaris extends active surveillance candidate population by 62% compared to clinical and pathologic features alone

Crawford, E D, et al. Cell cycle progression score and treatment decisions in prostate cancer: Results from an ongoing registry. Current Medical Research and Opinion 2014;30(6), 1025-1031
Local Coverage Determination (LCD):
MoIDX-CDD: Genomic Health™ Oncotype DX® Prostate Cancer Assay (L36368)

Local Coverage Determination (LCD):
MoIDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease (L37082)

Local Coverage Determination (LCD):
MoIDX-CDD: ProMark Risk Score (L36706)

Draft LCD for use of Decipher in men with very low and low NCCN risk prostate cancer

San Diego – July 24, 2018 – GenomeDx Biosciences, a leader in the field of urologic cancer genomics, today announced that Palmetto GBA, a Medicare Administrative Contractor (MAC), has issued a Draft local coverage determination (LCD) and completed the public comment period for use of the Decipher Prostate Biopsy genomic classifier in patients with very low and low NCCN risk prostate cancer. These men are candidates for active surveillance.
When to use
Summary

• Biomarkers now well validated for use in prostate cancer risk stratification
• Actionable results
• Not cheap but covered and significant ROI
• Precision medicine
• Not for every case, but for when you are on the fence