Prostate Cancer Genomics: What, When, and Which?

Judd W. Moul, M.D. FACS
James H Semans Professor of Surgery - Duke Cancer Institute
Duke University Medical Center
Durham, NC --- MAR 2017
Disclosures-Judd W Moul, MD-2015-2017

- Dendreon
- Janssen
- Ferring
- Medivation-Astellas
- Myriad Genetics
- Genomic Health
- Genome Dx
- Sanofi
- Theralogix
- Bayer
Localized CaP: Molecular Alterations in 74% of Patients

Figure 1. Genomic Highlights of Primary Prostate Cancer

- DNA repair genes—19%
  - BRCA1/2, CDK12, ATM, FANC2, RAD51C

- RAS or PI3K pathways—25%
  - PTEN, PIK3CA, PIK3CB, AKT1, MTOR, HRAS, RRAS2, RAC1, BRAF

Molecular alterations 74%
Alterations not identified 26%

Mutational load: Median 0.94 mutations/megabase
Some samples have more than 1 of these mutations

333 samples
Researchers: Genetic testing should be used more frequently for metastatic prostate cancer

Men with metastatic prostate cancer appeared significantly more likely to harbor germline mutations in DNA repair genes than those with localized disease, according to data published in The New England Journal of Medicine.

The frequency of germline mutations in men with prostate cancer — which did not differ according to age at diagnosis or family history of prostate cancer — suggests a need for routine genetic testing in this population.

“The result is surprising and important for men with prostate cancer, as this information may prioritize certain therapies,” Peter Nelson, MD, member of the division of human biology, clinical research and public health sciences at Fred Hutchinson Cancer Research Center, said in a press release. “It is also important for family members, as they may have inherited a gene that predisposes them to developing one of several types of cancer, and heightened awareness could enhance early detection and treatment. These findings present a compelling argument for updating prostate cancer guidelines to include germline DNA testing as a part of standard care for men with metastatic prostate cancer.”

Inherited mutations in DNA repair genes are associated with increased risks for lethal prostate cancer; however, whether their incidence warrants routine testing was not determined.

Nelson and colleagues identified 692 men with metastatic prostate cancer for whom family history of cancer and age at diagnosis had been unselected. They isolated germline DNA, using sequencing assays to assess mutations to 20 DNA repair genes associated with can-
mCRPC: Clinically Actionable Genetic Mutations in 89% of patients

**Figure 2.** Mutational Snapshot of mCRPC

- **Clinically actionable mutations** 89%
- AR-related—62.7%
  - PI3K pathway—49%
    - PTEN, PIK3CA/B, PIK3R1, AKT1
  - DNA repair pathway—28.7%
    - BRCA2/BRCA1, ATM, CDK12, MLH1, MSH2
  - CDK pathway—7%
    - CDKN2A/B, CDKN1B, CDK4

Mutational load: Median 4.4 mutations/megabase

150 samples
CRPC: Circulating Tumor Cell Molecular Genetic Characterization

New Technology to Characterize Circulating Tumor Cells Suggests Better Treatment Decision-Making in Prostate Cancer

By Alice Goodman

An early study showed that an experimental blood test (i.e., "liquid biopsy") that characterizes the phenotype and genomic characteristics of circulating tumor cells appears to have utility in personalizing treatment decisions for individual men with advanced prostate cancer. The assay—developed and perspacing the toxicities that may result from an ineffective treatment,” he added.

**Study Details**

The liquid biopsy was obtained from phlebotomy samples and characctered the heterogeneity of circulating tumor cells on a cell-by-cell basis associated with a poor response to androgen receptor-directed therapy with enzalutamide or abiraterone acetate.

Median progression-free survival in those treated with an AR-directed therapy, was 5 months for those with a high Shannon Index score vs 17 months for those with a low Shannon Index score. Overall survival was 9 months vs not yet reached, respectively ($P < .0001$).

No association was seen between Shannon Index score and response to taxane therapy. “Taxanes are usually a later line of therapy in patients who have more advanced disease,” Dr. Scher remarked.

Isolated circulating tumor cells ($n = 741$ cells isolated from 31 patients) were then analyzed for genotypic heterogeneity by gene-amplification studies. A subtype dubbed “Type K” was associated with poor outcomes. This subtype had a large nucleus, high nuclear entropy, and frequent nucleoli, he continued. This is a preliminary observation and will be studied further.

Future study by Dr. Scher and his colleagues will be aimed at locking down biomarkers, then demonstrating their clinical utility. “We plan to explore whether the heterogeneity score adds continued on page 30

---

**EXPERT POINT OF VIEW**

This platform has no selection bias. Phlebotomy samples are drawn at key decision points. We begin to see that heterogeneity of circulating tumor cells predicted for shorter progression and survival times with
Molecular Risk Tools-2017

**Serum Markers**
- PHI (Beckman Coulter)
- 4K Score (Opko Labs)

**Prostate Biopsy Tissue**
- Confirm MDx (MDx Health)
- Prolaris (Myriad Genetics)
- Oncotype GPS (Genomic Health)
- Decipher (Genome Dx)

**Radical Prostatectomy Tissue**
- Prolaris (Myriad Prolaris)
- Decipher (Genome Dx)
Genetic testing at Duke Prostate Center-Duke Cancer Institute

- Duke Diagnostic Technology Committee (multi-D) must approve all “send-out” molecular/genetic tests
- Myriad Prolaris approved 12/19/2012
- Oncotype Dx GPS approved 9/10/14
- 4K score rejected 12/2014
- Decipher (post RP) approved 6/2015
- PHI “in house” Duke Labs 1/2016
- Confirm MDx- approved 5/12/2016
The panel engaged in a long discussion regarding molecular testing. Many panel members expressed their excitement regarding the potential benefits of these tests, and many said they currently order them for their patients. However, the panel also discussed the data supporting the clinical utility of these tests and emphasized several points. First, no randomized clinical trial has yet assessed the clinical utility of these tests. Second, no test has been shown to be predictive of prostate cancer–specific outcomes in response to various management strategies. Finally, no head-to-head comparisons of these assays have been performed. Still, the panel pointed to data suggesting that test results may encourage men to choose active
The panel engaged in a long discussion regarding molecular testing. Many panel members expressed their excitement regarding the potential benefits of these tests, and many said they currently order them for their patients. However, the panel also discussed the data supporting the clinical utility of these tests and emphasized several points. First, no randomized clinical trial has yet assessed the clinical utility of these tests. Second, no test has been shown to be predictive of prostate cancer-specific outcomes in response to various management strategies. Finally, no head-to-head comparisons of these assays have been performed. Still, the panel pointed to data suggesting that test results may encourage men to choose active
Guidelines


Featured Updates to the NCCN Guidelines

The panel engaged in a long discussion regarding molecular testing. Many panel members expressed their excitement regarding the potential benefits of these tests, and many said they currently order them for their patients. However, the panel also discussed the data supporting the clinical utility of these tests and emphasized several points. First, no randomized clinical trial has yet assessed the clinical utility of these tests. Second, no test has been shown to be predictive of prostate cancer–specific outcomes in response to various management strategies. Finally, no head-to-head comparisons of these assays have been performed. Still, the panel pointed to data suggesting that test results may encourage men to choose active
The panel engaged in a long discussion regarding molecular testing. Many panel members expressed their excitement regarding the potential benefits of these tests, and many said they currently order them for their patients. However, the panel also discussed the data supporting the clinical utility of these tests and emphasized several points. First, no randomized clinical trial has yet assessed the clinical utility of these tests. Second, no test has been shown to be predictive of prostate cancer–specific outcomes in response to various management strategies. Finally, no head-to-head comparisons of these assays have been performed. Still, the panel pointed to data suggesting that test results may encourage men to choose active
“Unfortunately, the literature supporting the efficacy of DRE and biomarkers other than PSA for screening average risk men provided minimal evidence to draw conclusions.”

“The Panel identified four major areas where knowledge gaps prevented a precise assessment of the magnitude of screening benefits and the harms....... Fourth, direct evidence for any additional benefit of using DRE, PSA derivatives (PSA density, PSA kinetics, age adjusted PSA levels), PSA molecular forms (proPSA, freePSA, complexed PSA), novel urinary biomarkers (PCA3), or imaging as primary screening tests is absent.”
Molecular Risk Tools-2017

**Serum Markers**
- PHI (Beckman Coulter)
- 4K Score (Opko Labs)

**Prostate Biopsy Tissue**
- Confirm MDx (MDx Health)
- Prolaris (Myriad Genetics)
- Oncotype GPS (Genomic Health)
- Decipher (Genome Dx)

**Radical Prostatectomy Tissue**
- Prolaris (Myriad Prolaris)
- Decipher (Genome Dx)
• *phi* is a blood test that is reportedly more specific than PSA.

• *phi* score is calculated using an algorithm based on the results of these three assays:
  - PSA
  - Free PSA
  - p2PSA

• Results are reported on a scale of 0-100

• Cost $125

• FDA approved, but no specific billing code
**Indication for Use**

- **Men > 50 years of age**
- **Negative DRE**
- **PSA range of 4-10 ng/mL**

*NOTE: Different than EU labeling of PSA in range of 2-10 ng/mL*
Prostate Health Index (*phi*)

**phi Pivotal Trial Protocol**

**Endpoints:**

- Does *phi* improve specificity for detecting prostate cancer in the 4 to 10 ng/mL PSA range?
- Does *phi* improve the detection of prostate cancer relative to total PSA and % free PSA?

**Study Population & Inclusion Criteria:**

- 892 men
- PSA between 2-10 ng/mL
- 50 years or older
- Negative DRE

Prostate Health Index (\(phi\))

Clinical Study Results

- At 90% sensitivity, the specificity of \(phi\) was 31.1% compared to 10.8% for PSA.

- At \(phi\) cutoffs ranging from 27 to 55, the probability of cancer ranged from 9.8% to 50.1%.

- Biopsies could be avoided in 31% of men in the PSA range of 4-10 ng/ml with a PHI score of <27 (set at 90% sensitivity).
- *phi* included as a marker of specificity for PCA: A *phi* value of >35 is strongly suspicious for Pca

- However, just like PSA "cutpoints", the PHI upper limit of normal is controversial ranging from 21.3 (95% sensitivity) to 35
Molecular Risk Tools-2017

**Serum Markers**
- PHI (Beckman Coulter)
- 4K Score (Opko Labs)

**Prostate Biopsy Tissue**
- Confirm MDx (MDx Health)
- Prolaris (Myriad Genetics)
- Oncotype GPS (Genomic Health)
- Decipher (Genome Dx)

**Radical Prostatectomy Tissue**
- Prolaris (Myriad Prolaris)
- Decipher (Genome Dx)
Kallikrein markers may improve high-grade prostate cancer detection, reduce unnecessary biopsies

A statistical model using kallikrein markers better predicted high-grade prostate cancer in men with elevated PSA levels and reduced unnecessary biopsies compared with PSA level and age alone, according to the results of a prospective analysis.

"Risk of death from prostate cancer is strongly associated with levels of PSA in blood measured in middle-aged men," Hans Lilja, MD, PhD, of Memorial Sloan Kettering Cancer Center, and colleagues wrote. "Evidence from randomized screening trials in Europe shows that PSA-based screening can reduce deaths from prostate cancer, but also leads to overdiagnosis and the risk of overtreatment among elderly men with a limited life expectancy."

Previous retrospective studies identified four kallikrein markers — free PSA, intact PSA, total PSA and human kallikrein-related peptidase 2 (hK2) — that can predict biopsy outcomes, according to study background.

Lilja and colleagues evaluated the four kallikrein markers in cryopreserved blood samples from 6,138 men. The area under the curve for the kallikrein markers was significantly higher than the AUC for age and PSA level for predicting any-grade cancer and high-grade cancer.

The secondary analysis indicated use of the four markers would reduce the risk for unnecessary biopsy in 428 men and detect 119 instances of high-grade cancer. The risk for a delay in diagnosing high-grade cancer was relatively low (14 of 133).
Components of the 4Kscore Test

4Kscore Test

OPKO Platform

4 kallikrein levels
- Total PSA
- Free PSA
- Intact PSA
- hK2

+ Age, DRE, and prior biopsy status

OPKO ALGORITHM

4Kscore Test Results

% risk of having aggressive prostate cancer for an individual patient
4K Score (OPKO Diagnostics LLC)

- Cost approximately $400
- Use as a follow-up to abnormal PSA or DRE
- Predicts probability between <1%->95% for aggressive cancer e.g. Gleason >=7 on biopsy
- Predicts probability of metastases: 5/10/15/20 yrs:
  - Score <=7.5%: 0%/0.2%/1.0%/1.6%
  - Score >7.5%: 2.4%/5.6%/9.9%/16.4%
- www.4Kscore.com
4K Score (OPKO Diagnostics LLC)

- European 26 ctr. study-Parekh et al Eur Urol 2014
- N=1012 men referred for biopsy
- 54% biopsies negative; 46% positive; 23% \( \geq \) Gl 7
- 30-58% of biopsies could have been avoided, while only 1.3-4.7% of men would have been delayed in Dx of \( \geq \) Gl 7.
- 4K performed better than the PCPTRC 2.0 in predicting Gl \( \geq \) 7.
4K Score (OPKO Diagnostics LLC)

- American study of 35 academic and comm. Centers
- N=611 referred for biopsy
- Reduced number of biopsies by 64%
- Risk for aggressive cancer: <7.5%/7.5-19%/>20%
- In these groups, biopsies were reduced by 94%; 52.9%; and 19%, respectively
- Konety et al, Reviews in Urology, 2015
Molecular Risk Tools-2017

Serum Markers
- PHI (Beckman Coulter)
- 4K Score (Opko Labs)

Prostate Biopsy Tissue
- Confirm MDx (MDx Health)
- Prolaris (Myriad Genetics)
- Oncotype GPS (Genomic Health)
- Decipher (Genome Dx)

Radical Prostatectomy Tissue
- Prolaris (Myriad Prolaris)
- Decipher (Genome Dx)
ConfirmMDx detects an epigenetic field effect or “halo” associated with the cancerization process at the DNA level in cells adjacent to cancer foci. This epigenetic “halo” around a cancer lesion can be present despite having a normal appearance under the microscope. Henrique, et al. Mol Cancer Res 2006;4:1-8
Confirm MDx (MDx Health)

- The GSTP1 gene was thought to be epigenetically silenced by DNA methylation. This occurs in almost all prostate cancers.
- Methylation is a field effect.
- Can this biomarker identify those that do and that do not need a subsequent biopsy.
- The Confirm MDx test arose trying to commercialize it based upon it as a tissue marker.
- The high NPV should beat a baseline 25% chance for a positive subsequent biopsy.
Confirm MDx (MDx Health)

- They realized they could optimize the NPV by adding APC and Ras 1 to GSTP1.
- Technically difficult because bisulfite-based test is challenging with recovery of only 2% of DNA leading to many false negatives or in-evaluable patients.
- Limited sensitivity is the Achilles heel, but many are low-volume, low-risk tumors.
- You can detect this protein in the blood and in the urine, which is where this test will likely end up.
- Other companies working in this area are Epigenomics and Veridex.
- Reimbursed by Medicare.
Molecular Risk Tools-2017

**Serum Markers**
- PHI (Beckman Coulter)
- 4K Score (Opko Labs)

**Prostate Biopsy Tissue**
- Confirm MDx (MDx Health)
- Prolaris (Myriad Genetics)
- Oncotype GPS (Genomic Health)
- Decipher (Genome Dx)

**Radical Prostatectomy Tissue**
- Prolaris (Myriad Prolaris)
- Decipher (Genome Dx)
## Prolaris or Oncotype for Active Surveillance vs. Active Treatment Decisions

<table>
<thead>
<tr>
<th>Technique</th>
<th>Prolaris</th>
<th>Oncotype DX</th>
<th>Prostate Cancer Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT-PCR</strong></td>
<td>RT-PCR 31 genes</td>
<td>RT-PCR 12 genes</td>
<td></td>
</tr>
<tr>
<td>Clinical Endpoint</td>
<td>10-year untreated PCSM</td>
<td>Adverse pathology risk</td>
<td>5-year BCR risk</td>
</tr>
<tr>
<td></td>
<td>10-year BCR risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample</td>
<td>Biopsy Cores Prostatectomy Specimen</td>
<td>Biopsy Cores</td>
<td></td>
</tr>
</tbody>
</table>
**Prolaris or Oncotype for Active Surveillance vs. Active Treatment Decisions**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Prolaris</th>
<th>Oncotype DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT-PCR</td>
<td>RT-PCR</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>31 genes</td>
<td>12 genes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Endpoint</th>
<th>Prolaris</th>
<th>Oncotype DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-year untreated PCSM</td>
<td>10-year BCR risk</td>
<td>Adverse pathology risk</td>
</tr>
<tr>
<td>10-year BCR risk</td>
<td></td>
<td>5-year BCR risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample</th>
<th>Prolaris</th>
<th>Oncotype DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy Cores</td>
<td>Biopsy Cores</td>
<td></td>
</tr>
<tr>
<td>Prostatectomy Specimen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Utility:**
- Active Surveillance / Watchful Waiting vs Intervention
  - Gleason 6, unsure of management
  - Low Volume of Gleason 7
  - Gleason 7/8 in elderly
Myriad Prolaris: Use to help decide between active surveillance and active treatment

### CCP Gene Function

#### THE PROLARIS 46-GENE PANEL

<table>
<thead>
<tr>
<th>Cell Cycle Progression Genes</th>
<th>Housekeeper Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOXM1, CDC20, CDKN3, CDC2, KIF11, KIAA0101, NUSAP1, CENPF, ASPM, BUB1B, RRM2, DLGAP5, BIRC5, KIF20A[BP1], PLK1, TOP2A, TK1, PBK, ASF1B, C18orf24, RAD54L, PTTG1, MCM10, PRC1, DTL, CEP55, RAD51, CENPM, CDCA3, CDCA8, ORC6L</td>
<td>RPL38, UBA52, PSMC1, RPL4, RPL37, RPS29, SLC25A3, CLTC, TXNL1, PSMA1, RPL8, MMADHC, RPL13A, PPP2CA, MRFAP1</td>
</tr>
</tbody>
</table>

**31 Cell Cycle Progression Genes**
Highly correlated and provide a reproducible measure of cell proliferation

**15 Housekeeper Genes**
Normalize the expression of the cell proliferation genes
Myriad Prolaris Validation

DEVELOPMENT AND VALIDATION OF THE PROLARIS TEST

- Prostate Cancer Technical Feasibility (n=96)
- Gene Selection Study
- Finalized Signature 46 Gene Assay
- Biopsy Validation (n=349)
- TURP Validation (n=337)
- Post RP 1 Validation (n=353)
- Post RP 2 Validation (n=413)

Data on file, Myriad Genetics, Inc.
Myriad Prolaris Biopsy validation

- Six cancer registries in Great Britain
- Men with localized prostate cancer
- Conservatively managed without initial intent for curative treatment
- End point was time to prostate cancer death

### Myriad Prolaris-Biopsy-PCSS

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=349</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endpoint</strong></td>
<td>PCA specific death</td>
</tr>
<tr>
<td><strong>Events-PCSS</strong></td>
<td>90 (26%)</td>
</tr>
<tr>
<td><strong>Median years follow-up</strong></td>
<td>11.8 (10.8, 12.7)</td>
</tr>
<tr>
<td><strong>Median age</strong></td>
<td>71 (66, 73)</td>
</tr>
<tr>
<td><strong>Gleason</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>106 (30%)</td>
</tr>
<tr>
<td>7</td>
<td>152 (44%)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>91 (26%)</td>
</tr>
<tr>
<td><strong>Median PSA</strong></td>
<td>21.4 (11.9, 42)</td>
</tr>
</tbody>
</table>

**Myriad Prolaris: Multivariable Analysis of Prostate Cancer Mortality**

### Prediction Significance (Multivariate Analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolaris Score</td>
<td>1.65 (1.31, 2.09)</td>
<td>.000026</td>
</tr>
<tr>
<td>Gleason</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>0.61 (0.32, 1.16)</td>
<td>.0005</td>
</tr>
<tr>
<td>7</td>
<td>1 (ref)</td>
<td>---</td>
</tr>
<tr>
<td>&gt;7</td>
<td>1.90 (1.18, 3.07)</td>
<td>---</td>
</tr>
<tr>
<td>PSA</td>
<td>1.37 (1.05, 1.79)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

- Prolaris most significant predictor of PCa mortality

### Independence (by Pearson Correlation)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prolaris CCP Score Correlation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason</td>
<td>0.37 (0.27, 0.45)</td>
</tr>
<tr>
<td>Log (1 + PSA)</td>
<td>0.14 (0.04, 0.25)</td>
</tr>
<tr>
<td>Extent of disease</td>
<td>0.29 (0.19, 0.39)</td>
</tr>
</tbody>
</table>

- Prolaris is an independent predictor (i.e. not strongly correlated with clinical variables)

Myriad Proscar biopsy score distribution in clinical patients: 54% had change in Risk Assessment

<table>
<thead>
<tr>
<th>AUA Risk Classification</th>
<th>Considerably Less Aggressive</th>
<th>Less Aggressive</th>
<th>Consistent</th>
<th>More Aggressive</th>
<th>Considerably More Aggressive</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>12 (2.1%)</td>
<td>142 (24.4%)</td>
<td>277 (47.5%)</td>
<td>137 (23.5%)</td>
<td>15 (2.6%)</td>
<td>583</td>
</tr>
<tr>
<td>Intermediate</td>
<td>16 (2.2%)</td>
<td>195 (26.4%)</td>
<td>330 (44.6%)</td>
<td>168 (22.7%)</td>
<td>31 (4.2%)</td>
<td>740</td>
</tr>
<tr>
<td>High</td>
<td>12 (4.3%)</td>
<td>71 (25.3%)</td>
<td>107 (38.1%)</td>
<td>67 (23.8%)</td>
<td>24 (8.5%)</td>
<td>281</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>40 (2.5%)</td>
<td>408 (25.4%)</td>
<td>714 (44.5%)</td>
<td>372 (23.2%)</td>
<td>70 (4.4%)</td>
<td>1604</td>
</tr>
</tbody>
</table>

More than half of Proscar tests result in scores higher or lower than expected based on clinical features alone.
Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort

J Cuzick¹, S Stone², G Fisher¹, Z H Yang¹, B V North¹, D M Berney³, L Beltran³, D Greenberg⁴, H Møller⁵, J E Reid², A Gutin², J S Lanchbury², M Brawer² and P Scardino⁶ on behalf of the Transatlantic Prostate Group

¹Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK; ²Myriad Genetics, Inc., Salt Lake City, UT, USA; ³Department of Molecular Oncology, Barts Cancer Institute, Queen Mary University of London, London, UK; ⁴National Cancer Registration Service (Eastern Office), Public Health England, Cambridge, UK; ⁵Cancer Epidemiology and Population Health, King’s College London, London, UK and ⁶Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

- N=761, localized CaP, PSA < 100ng/mL
- Myriad Prolaris on needle bx cores
- Outcomes: CSS and OS
- Comparison with CAPRA score
Molecular Risk Tools-2017

- Serum Markers
  - PHI (Beckman Coulter)
  - 4K Score (Opko Labs)
- Prostate Biopsy Tissue
  - Confirm MDx (MDx Health)
  - Prolaris (Myriad Genetics)
  - Oncotype GPS (Genomic Health)
  - Decipher (Genome Dx)
- Radical Prostatectomy Tissue
  - Prolaris (Myriad Prolaris)
  - Decipher (Genome Dx)
Genomic Health GPS: Use to help determine between active treatment and active surveillance

**Oncotype DX Prostate**

- Quantitative 17-gene RT-PCR assay on manually micro dissected 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

**Androgen Signaling**
- AZGP1
- FAM13C
- KLK2
- SRD5A2

**Cellular Organization**
- FLNC
- GSN
- GSTM2
- TPM2

**Stromal Response**
- BGN
- COL1A1
- SFRP4

**Proliferation**
- TPX2

**GPS**

\[
0.735 \times \text{Stromal Response group} - 0.352 \times \text{Androgen Signaling group} + 0.095 \times \text{Proliferation group} - 0.368 \times \text{Cellular Organization group}
\]

Scaled between 0 and 100

Cooperberg MR, et al. Development and validation for the biopsy-based genomic prostate score (GPS) as a predictor of high grade or extracapsular prostate cancer to improve patient selection for active surveillance. Presented at AUA 2013
The Oncotype DX® Prostate Cancer Assay

WHAT is the test?
• A tumor gene expression assay which produces a Genomic Prostate Score (GPS) to help guide initial treatment decisions at the time of biopsy.

HOW are the results reported?
• Favorable Pathology: freedom from high-grade (dominant pattern 4 or any pattern 5) and/or non-organ-confined disease

WHO is the test for?
• Men with low to low-intermediate risk prostate cancer (GS 3+3, low volume 3+4)

WHY do the test?
• To improve risk stratification by incorporating individual underlying tumor biology
• To identify appropriate patients for Active Surveillance (AS) or immediate treatment

Laboratory Director: Patrick Joseph, MD

*This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are subjective to the ordering physician’s discretion.
Oncotype GPS Validation Studies in RP patients - European Urology

First Validation Study

A 17-gene Assay to Predict Prostate Cancer Aggressiveness in the Context of Gleason Grade Heterogeneity, Tumor Multifocality, and Biopsy Undersampling


Second Validation Study

A Biopsy-based 17-gene Genomic Prostate Score Predicts Recurrence After Radical Prostatectomy and Adverse Surgical Pathology in a Racially Diverse Population of Men with Clinically Low- and Intermediate-risk Prostate Cancer

Objectives:

- To validate GPS as a predictor of adverse pathology in a contemporary clinically low risk patient cohort.

- To determine whether GPS adds independent predictive information beyond standard clinical and pathologic data.
Oncotype Risk Discrimination with Addition of GPS to NCCN

Multivariate Analysis
NCCN p-value = 0.002
GPS p-value = 0.001

In patients with Very Low, Low and Low-Intermediate risk prostate cancer, the GPS has been prospectively validated as a biopsy-based predictor of adverse pathology.

The GPS adds independent predictive information beyond standard clinical and pathological measures.

The GPS assesses underlying biology from very small biopsy tumor volumes, addressing issues of tumor heterogeneity and biopsy undersampling to more accurately predict disease aggressiveness.

Incorporation of the GPS enables more accurate identification of a larger population of patients who can more confidently choose active surveillance or immediate therapy as an initial management strategy.

Klein et al Conclusions
Primary objective:
- Determine if GPS can predict the time to biochemical recurrence (BCR) after RP

Secondary objectives:
- Confirm that GPS can predict the likelihood of adverse pathology (AP) at RP
- Determine if GPS is associated with development of metastatic disease

Key Exploratory objective:
- Compare the performance of GPS in African-American and Caucasian patients
Confirmed biopsy GS 6 or 7 (Central pathology review) N=431

Patients with available biopsy tissue N=500

Confirmed biopsy GS 6 or 7 (Central pathology review) N=431

Final evaluable population for BCR endpoint N=402

Evaluable population for AP endpoint N=382

69 (14%) excluded based on central pathology review:
Insufficient or no tumor (n=56) Biopsy GS > 7 (n=13)

29 (7%) excluded for insufficient RNA quality

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


*Center for Prostate Disease Research (CPDR), Rockville, MD

**Walter Reed National Military Medical Center and Madigan Army Medical Center an equal access healthcare system

NCCN is a registered trademark of the National Comprehensive Cancer Network, which does not endorse any product or therapy.
### Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at Diagnosis</strong></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>41-76</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>305</td>
<td>(76%)</td>
</tr>
<tr>
<td>African-American</td>
<td>82</td>
<td>(20%)</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>( 4%)</td>
</tr>
<tr>
<td><strong>PSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>92</td>
<td>(23%)</td>
</tr>
<tr>
<td>4-9.99</td>
<td>273</td>
<td>(68%)</td>
</tr>
<tr>
<td>10-20</td>
<td>37</td>
<td>( 9%)</td>
</tr>
<tr>
<td><strong>Clinical T-Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>276</td>
<td>(69%)</td>
</tr>
<tr>
<td>T2</td>
<td>126</td>
<td>(31%)</td>
</tr>
<tr>
<td><strong>Biopsy Gleason Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+3</td>
<td>295</td>
<td>(73%)</td>
</tr>
<tr>
<td>3+4</td>
<td>94</td>
<td>(23%)</td>
</tr>
<tr>
<td>4+3</td>
<td>13</td>
<td>( 3%)</td>
</tr>
<tr>
<td><strong>NCCN Risk Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Low</td>
<td>43</td>
<td>(11%)</td>
</tr>
<tr>
<td>Low</td>
<td>210</td>
<td>(54%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>139</td>
<td>(36%)</td>
</tr>
</tbody>
</table>

- Distribution of baseline characteristics was representative of a contemporarily managed population of men with prostate cancer

Clinical events

- **163 (43%) 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)
  - Capsular incision (pT2+) was considered non-organ-confined disease

- **62 (15%) BCR after RP**
  - Defined as either two successive PSA level $\geq 0.2$ ng/mL ($n=57$) \(^1\), or the initiation of salvage therapy after a PSA rise ($n=5$)

- **5 (1%) distant metastases**
  - Confirmed by biopsy or imaging

---

Distribution of Surgical Gleason Scores and Pathologic T-stage on Central Pathology Review

<table>
<thead>
<tr>
<th>RP Gleason Score</th>
<th>Pathologic T-Stage</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2 n (%)</td>
<td>T2⁺ n (%)</td>
<td>T3 n (%)</td>
<td>Total n (%)</td>
<td></td>
</tr>
<tr>
<td>3+3</td>
<td>170 (45)</td>
<td>18 (5)</td>
<td>25 (7)</td>
<td>213 (56)</td>
<td></td>
</tr>
<tr>
<td>3+4</td>
<td>49 (13)</td>
<td>9 (2)</td>
<td>31 (8)</td>
<td>89 (23)</td>
<td></td>
</tr>
<tr>
<td>Any major pattern 4 or tertiary pattern 5</td>
<td>33 (9)</td>
<td>12 (3)</td>
<td>35 (9)</td>
<td>80 (21)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>252 (66)</td>
<td>39 (10)</td>
<td>91 (24)</td>
<td>382 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Percentages may not add up to 100% due to rounding

- 163 (43%) patients had adverse pathology at RP
- 33 (9%) patients had high Gleason Score disease only
- 83 (22%) had high stage (T2+ or T3) disease only
- 47 (12%) patients had both high grade & stage Gleason Score

A wide distribution of GPS results within different clinical sub-groups

- A broad and overlapping range of GPS results was observed within each NCCN risk group and age quartile.
- GPS had a modest correlation with NCCN risk group ($r=0.37$) and age ($r=0.26$).

• Ability of Onco\textit{type} DX GPS to predict multiple clinically relevant endpoints, both near-term and longer-term outcomes, establishes the assay as an independent measure of PCa aggressiveness.

• The study confirms the findings of the first validation study showing GPS as a predictor of adverse surgical pathology, a clinically actionable endpoint.

• GPS is now validated as a predictor of BCR following RP.

• Association between GPS and metastasis was statistically significant.

• In this equal access healthcare system, GPS was predictive of outcome in both Caucasian and African-American men.
Comparison of two genetic tissue tests

Myriad Prolaris

- RNA expression of cell cycle progression (CCP) genes
- 31 genes across cell cycle progression pathways
- 15 housekeeper genes
- Each 1 unit change in Prolaris score equals a doubling (or halving) of risk
- Predicts DSS, PSAR
- Biopsy tissue
- Radical prostatectomy tissue
- 7 publications

Genomic Health GPS

- RNA expression of multiple cellular pathways
- 12 genes across multiple varied cellular pathways
- 5 housekeeper genes
- GPS results range from 0-100
- Newly diagnosed men with low to low-intermediate risk prostate cancer (GS 3+3, low volume 3+4) who have had a biopsy within the past 12 months
- Predicts adverse pathology
- 2 publications
Limitations of Prolaris/Oncotype

- Neither have been prospectively validated in an active surveillance population.
- Unclear which of the two is “better.”
- Costly ($3,000-3,500 USD)
- How the information is presented to the patient is not standardized and physician biases and patient wishes will invariably affect treatment decisions.
- Not globally available.
Molecular Risk Tools-2017

Serum Markers
- PHI (Beckman Coulter)
- 4K Score (Opko Labs)

Prostate Biopsy Tissue
- Confirm MDx (MDx Health)
- Prolaris (Myriad Genetics)
- Oncotype GPS (Genomic Health)
- Decipher (Genome Dx)

Radical Prostatectomy Tissue
- Prolaris (Myriad Prolaris)
- Decipher (Genome Dx)
Molecular Risk Tools-2016

Serum Markers
- PHI (Beckman Coulter)
- 4K Score (Opko Labs)

Prostate Biopsy Tissue
- Confirm MDx (MDx Health)
- Prolaris (Myriad Genetics)
- Oncotype GPS (Genomic Health)
- Decipher (Genome Dx)

Radical Prostatectomy Tissue
- Prolaris (Myriad Prolaris)
- Decipher (Genome Dx)
Molecular Risk Tools-2016

Serum Markers
- PHI (Beckman Coulter)
- 4K Score (Opko Labs)

Prostate Biopsy Tissue
- Confirm MDx (MDx Health)
- Prolaris (Myriad Genetics)
- Oncotype GPS (Genomic Health)
- Decipher (Genome Dx)

Radical Prostatectomy Tissue
- Prolaris (Myriad Prolaris)
- Decipher (Genome Dx)
# Post-Radical Prostatectomy

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technique</strong></td>
<td>RNA microarray assay 1.4 million regions</td>
</tr>
<tr>
<td><strong>Clinical Endpoint</strong></td>
<td>5- and 10-year post-RP metastatic risk</td>
</tr>
<tr>
<td><strong>Sample</strong></td>
<td>Prostatectomy Specimen</td>
</tr>
</tbody>
</table>
Post-Radical Prostatectomy

| Technique       | RNA microarray assay  
|                | 1.4 million regions  |
| Clinical Endpoint | 5- and 10-year post-RP metastatic risk |
| Sample          | Prostatectomy Specimen |

Clinical Scenes:
- Adverse pathology on RP specimen - need for more information
- Rising PSA after RP – biochemical vs benign recurrence
Diagnosis  Surgery  Adjuvant Therapy  Salvage Therapy

Decipher Genome Dx) Genomic Classifier (GC)
Decipher

- Radical Prostatectomy archival tissue
- Multi-Plex “gene chip” technology- 22 gene “genomic classifier” (GC)
- Medicare reimbursed
- Up to 4 years post RP
- Indication: Adverse pathology

Observe vs Treat?  Early vs. Late?  Clinical Trials?
Adjuvant vs Salvage?  RT vs ADT?  RT vs RT + ADT?
Decipher

- 22 marker classifier
- 219 pts – 69 w/ mets at median f/u 6.7 yrs
- BCR @ 3 yrs = 35%
- Metastatic Dz @ 5 yrs = 6%
Decipher

- 20% of pts had GC > 0.6 and 22.5% 5 yr cumulative incidents of mets
- 60% of pts had GC < 4 and 2.4% 5 yr cumulative incidence of mets

Karnes et al., Journal of Urology 2013
Decipher Sample Report

Patient's Decipher Risk

60.0%
High risk (> 8.5%)

8.5%
Average risk*

6.0%
Low risk (<4.4%)

4.4%

1.8% Probability of metastasis at 5 years

Summary of Results

Interpretation: Lower than average risk

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s Decipher Risk</td>
<td>1.8%</td>
</tr>
<tr>
<td>Cohort Average Risk*</td>
<td>6.0%</td>
</tr>
<tr>
<td>Relative Risk (Decipher/Average)</td>
<td>0.3X</td>
</tr>
</tbody>
</table>

Decipher Test Result: Decipher probability of developing clinical metastasis within five years of radical prostatectomy: 1.8% (0.3 times the average risk observed in a clinical study of high risk patients).

Comments: Decipher indicates a patient’s probability of developing clinical metastasis within five years of a radical prostatectomy. The average risk for clinical metastasis by five years after radical prostatectomy for clinically high-risk men is 6.0%. The Decipher risk reported here has a 95% confidence interval of 0.8% to 2.8%, which is lower than the average risk and therefore patient is considered to have a lower than average risk of clinical recurrence within that time frame.
Genomic Test Identifies Patients With Prostate Cancer in Need of Intensified Salvage Therapy

By Alice Goodman

Prostate cancer has been slow to catch up with breast cancer in terms of using biomarkers, but a new study represents progress in this regard. A genomic classifier called Decipher® provides important information that can be used to make treatment decisions for men with prostate cancer and a rising prostate-specific antigen (PSA) after radical prostatectomy. The genomic classifier was able to distinguish between low-risk and high-risk men in this setting who received salvage radiation therapy (with or without hormonal therapy). Results were presented at the 2015 ASTRO Annual Meeting.¹

With current standard practice, cancer. Genomic Prostate Score (GPS) is used prior to treatment, whereas Decipher is performed after surgical resection. The third test, Proarris, can be used before or after surgery.

The Decipher test, which analyzes a small tissue sample obtained during prostatectomy, has been approved by Medicare for reimbursement. Dr. Den said he uses it routinely in his clinical practice and that it is being adopted across the country.

In an interview with The ASCO Post, Dr. Den explained that the Decipher platform uses a chip with 1.4 million markers containing coding and non-coding genes. The genomic classifier clinical trials. About 20% were on concurrent hormone therapy as part of their salvage treatment. Eighty percent had clear surgical margins following prostatectomy.

Salvage radiotherapy was defined as radiotherapy given if the PSA level was > 0.2 ng/mL or after salvage androgen-deprivation therapy. Early salvage radiation therapy was defined as given incidence of metastasis at this time point.

The study was not without limitations. It was a retrospective analysis and did not allow for analysis of cancerspecific mortality.

‘The Wave of the Future’
ASTRO Incoming President David Beyer, MD, of the Cancer Centers of
Genomic Classifier Identifies Men With Adverse Pathology After Radical Prostatectomy Who Benefit From Adjuvant Radiation Therapy


ABSTRACT

Purpose
The optimal timing of postoperative radiotherapy (RT) after radical prostatectomy (RP) is unclear. We hypothesized that a genomic classifier (GC) would provide prognostic and predictive insight into the development of clinical metastases in men receiving post-RP RT and inform decision making.

Patients and Methods
GC scores were calculated from 188 patients with pT3 or margin-positive prostate cancer, who received post-RP RT at Thomas Jefferson University and Mayo Clinic between 1990 and 2009. The primary end point was clinical metastasis. Prognostic accuracy of the models was tested using the concordance index for censored data and decision curve analysis. Cox regression analysis tested the relationship between GC and metastasis.
Decipher (Genome Dx)- JCO Highlights

- Decipher **high risk patients** who received adjuvant RT had 80% reduction in metastasis risk compared to those who received salvage RT. (hazard ratio)

- Decipher **low risk patients** showed no difference in metastasis at 5 years for salvage or adjuvant.

- Decipher is a superior prognostic indicator for predicting metastasis in patients treated with radiotherapy compared to the CAPRA-S nomogram.

- Decipher reclassified 43% of intermediate and high risk CAPRA-S patients to low risk, with 96% metastasis-free survival.
Decipher - JCO Highlights

- Provide therapy to those most likely to benefit
- Spare the appropriate patients from unnecessary treatment and side effects.

<table>
<thead>
<tr>
<th>Decipher Risk</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>Likely to experience significantly lower incidence (80%) of metastasis with adjuvant radiation therapy</td>
</tr>
<tr>
<td>LOW</td>
<td>Managed safely with observation until PSA rise (if any)</td>
</tr>
</tbody>
</table>

Decipher low-risk patients can be managed safely with observation until PSA rise

Decipher high risk patients experience lower rates of metastasis when treated with adjuvant radiation post RP

![Graph showing cumulative incidence of metastasis](Image)
Molecular Genetic Markers - Summary

- Hot topic!
- Growing list of commercially available molecular tests in prostate cancer
- PHI and 4K Score - new blood tests to augment PSA
- Myriad Prolaris and Genomic Health Oncotype GPS - Biopsy tissue based mRNA multi-gene expression/ archival tissue: AS vs Active Rx
- Decipher genomic classifier post RP
- Confirm MDx for high risk but negative biopsy