Putting the PSA in Perspective

AND - New Biomarkers to Support Personalized Decision-making Along the Continuum of Care
History of the PSA

- Approved by the FDA in 1986 to monitor disease progression for men already diagnosed
- Approved in 1994 to screen for the possible presence of prostate cancer
- Sensitive, not specific...
- Since its introduction as a screening tool, each year:
  - about 2,500 lives are spared due to early detection.
  - About 100,000 men are subjected to aggressive treatment with no lifesaving benefit, and sometimes serious quality of life consequences.
- How to best administer the PSA is an evolving science.
- PSA is a gateway screening tool to newer and much more advanced biomarkers that help personalize care and reduce unnecessary pain and suffering.
Current Recommendations

- **USPSTF**: Doctors should discuss prostate screening with male patients.

- **National Comprehensive Cancer Network (NCCN)**: A man having a baseline PSA of more than 1.0 ng/mL in his 40s is at the greatest risk of the future development of advanced prostate cancer.
Urine and Blood Biomarkers

Prostate cancer biomarkers:
- miRNAs
- Exosomal biomarkers
- PCA3 score
- TMPRSS2:ERG fusion gene

LUMEN:
- Exosomal biomarkers
- 4Kscore
- Total PSA
- Free PSA
- iPSA
- hK2

BLOOD:
- miRNAs
- Prostate Health Index
- Total PSA
- [−2]proPSA
- Free PSA
Biomarkers for Early Detection

- Prostate-specific antigen (PSA)*
- Prostate Health Index (phi)*
- PCA3
- 4Kscore
- SelectMDx
- ERG Protein Tissue Marker
Prostate Specific Antigen (PSA)
Prostate Health Index (PHI)

- Risk Factors
- PSA Test
- Monitoring
- Prostate Biopsy

**DIAGNOSTIC GAP**

- Prostate Health Index -> phi™
  - Pro[2]PSA
  - Free PSA
  - Total PSA

- Complexed PSA
- Free PSA 15%
- Pro[2]PSA 10%
- BPH-A 28%
PCA3

Detection of Cancer Cells Directly

Step 1: PSA & PCA3 mRNA anneals to complementary DNA primers attached to magnetic particles

Step 2: The mRNA is amplified using reverse transcription PCR

Step 3: The mRNA is detected using chemiluminescent probe

PCA3 Score = \frac{PCA3 mRNA}{PSA mRNA} \times 1000

Increased Probability of Positive Biopsy

Decreased Probability of Positive Biopsy
4K Score

4 Kallikreins

Components

- Total PSA
- Free PSA
- Intact PSA
- hK2

Results

- % risk of having aggressive prostate cancer
- For an individual patient

Outperforms PSA

The 4Kscore™ Test has the accuracy of a prostate biopsy for aggressive prostate cancer

2015 NCCN Prostate Cancer Early Detection Guidelines

When to use the 4Kscore Test*

- Suspicion of malignancy based on clinical findings or abnormal PSA
- Prior to 1st biopsy

- Prior to previous negative biopsy

- Order 4Kscore to identify the patient's individual risk of high grade, Gleason 7 or higher cancer on prostate biopsy

- Low Risk; continue to follow

- High Risk; additional evaluation or biopsy

*Not indicated in men who:

- Have a diagnosis of prostate cancer
- Are taking 5-alpha-reductase inhibitors within the last 6 months
- Have recently undergone a prostate procedure within the last 6 months
SelectMDx helps identify men at increased risk for aggressive cancer

Implements patient risk stratification for prostate biopsy

Routine Screening → Elevated PSA, Abnormal DRE → SelectMDx

- Increased Risk for GS ≥ 7 PCa → Consider Biopsy
- Very Low Risk for GS ≥ 7 PCa → Avoid Biopsy

For patients being considered for initial prostate biopsy:
- Identify men at high risk for aggressive cancer
- Assay performed on non-invasive, urine sample

Very Low Risk:
- 99.6% NPV for GS ≥8
- 98% NPV for GS ≥7

Likelihood for prostate cancer upon biopsy:
- 10% for 8% likelihood of low grade prostate cancer and 2% likelihood of high grade prostate cancer
- 85% for 35% likelihood of low grade prostate cancer and 50% likelihood of high grade prostate cancer
Biomarkers for Confirming Need for Repeat Biopsy

- PCA3*
- 4Kscore
- ConfirmMDx
- Know Error®
Confirm MDx

Epigenetic Changes Influence Gene Expression Without Changing the Genome

- **ConfirmMDx™** for Prostate Cancer detects an epigenetic field effect with the “cancerization” process at the DNA level.

- This **field effect** around the cancer lesion can be present despite the normal appearance of cells.

- Detection of field effects extends the coverage of the biopsy helping to rule in, or rule out, occult cancers.
Complete with Know Error

A New Study by the INSTITUTE of MEDICINE Reveals...

- 5% of diagnoses are in error, translating to...
- 5% IOM ambulatory error rate
- 20 Average number of patient visits per physician per day
- 34% Percentage of visits involving a diagnostic question
- 62 Average number of diagnostic errors per physician per year
- 184 Average number of days worked per year per physician
- 3,680 Patient visits per year per physician
- 295,000 Number of primary care physicians, NPs and PAs in the United States
- 18,437,000 Estimated number of primary care diagnostic errors per year in the United States

Know Error
Biomarkers for Treatment Decision Support

- Gleason Score*
- Know Error®
- Oncotype DX
- Prolaris
- PTEN
- ProMarkTM
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<tr>
<td>1</td>
<td>Nearly normal cells</td>
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<td>3</td>
<td>Many abnormal cells</td>
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<tr>
<td>4</td>
<td>Very few normal cells left</td>
</tr>
<tr>
<td>5</td>
<td>Completely abnormal cells</td>
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</tbody>
</table>
Oncotype DX
Considerably Less Aggressive
Than Average AUA Intermediate Risk

PROLARIS SCORE 2.0

US Distribution Percentile: 2%
(For AUA Intermediate Risk)
Interpretation: 2% of patients in the AUA Intermediate Risk^ category have a lower Prolaris Score.

Mortality Risk

Mortality Risk: 1.7% 10-Year Prostate Cancer-Specific

Disease Specific Mortality
This patient’s 10-year risk of prostate cancer-specific mortality is 1.7% (95% CI 0.6-3.1%) with conservative management. Mortality risks could be altered by various therapeutic interventions. **

In a clinical study estimating 10-year prostate cancer-specific mortality risks for men undergoing conservative management, there were no observed prostate cancer deaths in patients with a predefined clinical risk score (SCPx combined with CAPRA) corresponding to a 2.3% (95% CI 1.1-4.3%) prostate cancer-specific mortality risk. **

Metastasis Risk

Metastasis Risk: 3.0% 10-Year (with definitive treatment)

Metastasis
This patient’s risk of metastasis within 10 years of diagnosis is 3.0% (95% CI 1.3-6.9%) after definitive treatment. ****
For example:

Low risk: 27% is risk of aggressive disease in men with Gleason 3+3 or 3+4 biopsies.

High risk:

- 0% is your risk of aggressive disease with a ProMark score of 30.

If diagnosed with prostate cancer and a Gleason score of 3+3 or 3+4, your risk of aggressive disease is 27%. With a ProMark score of 30, your risk of aggressive disease decreases from 27% to 15%.
Biomarkers for Considering the Need for Additional Treatment

- Decipher
- Prolaris
Patient Details
Patient Name: John 13 Doe
Medical Record Number: 123456789
Date of Birth: 01/01/1940
Date of Prostatectomy: 06/01/2014

Clinical Details
Pathology Report Date: 01/28/2013
Referring Pathologist/Laboratory: X

Order Information
Order Date: 09/15/2014
Ordering Physician: X
Clinic/ Hospital: Y

Specimen Received Date: 09/30/2014
GenomeDx Accession ID: DEC14968
Specimen ID: Lab09375

Pre-operative PSA (ng/mL): via
Gleason Score (Surgical Pathology): 4+5
- EPE
- SVI
- Stn-
- Uni
- BCR

Decipher Result: Genomic low risk

Summary of Decipher genomic risk results

Decipher 5 year risk of metastasis: 2.9%

Genomic risk of developing metastasis within five years of radical prostatectomy is 2.9%, the average clinical risk for a patient with adverse pathology.

Comments: Decipher indicates a patient’s probability of developing metastasis within 5 years of a radical prostatectomy. The average risk for metastasis by 5 years after surgery for clinically high-risk men is 6.0%. The Decipher risk reported here has a 95% confidence interval of 1.6% to 4.2%, which is significantly lower than average clinical risk and therefore the patient is considered to have a lower than average risk of clinical recurrence within 5 years.

Average clinical risk refers to the average asymptomatic clinical high-risk men post surgery established in a cohort of 1,600 disease high-risk patients that received radical prostatectomy as first the treatment of the Mayo Clinic between 2000 and 2008. The average incidence of metastases was 6.0% at 5 years post radical prostatectomy.

3.2 Year Prostate Specific Acid (PSA) Recurrence Rate. A genomic risk score is derived by analyzing the PSA expression of 21 families in a primary prostate cancer cohort from the Mayo Clinic. This score provides a way to predict the risk of disease progression. The score is based on a statistical analysis of gene expression patterns in prostate tissue.

The score ranges from 0 to 39. A score of 0-10 is considered low risk, 11-20 is considered intermediate risk, and 21-39 is considered high risk.

For patients with a score of 21-39, the 3.2 year PSA recurrence rate is 15%.

GenomeDx Medical Director (Name & Signature)
Medical Directors: Timothy T. Ticho, MD PhD, Doug DelGreco, MD

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<th>Test</th>
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<tr>
<td>PCA3 (early detection)</td>
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<tr>
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<td>Select MDx</td>
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<tr>
<td>ERG Protein Tissue Marker</td>
<td>? (call 800-428-5074)</td>
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<td>Confirm MDx</td>
<td>$3,300 (60% discount for uninsured)</td>
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<td>Know Error</td>
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<tr>
<td>Oncotype DX</td>
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<tr>
<td>Prolaris</td>
<td>$375 (assistance programs on website)</td>
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<tr>
<td>PTEN</td>
<td>$249</td>
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<tr>
<td>ProMark TM</td>
<td>~$350 (call 877-743-3338)</td>
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<tr>
<td>Decipher</td>
<td>$699</td>
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Take Home Message

● The science of early detection and decision support is rapidly evolving.

● Discussions should occur on an individual and personalized basis.

● Men need to know what tests to ask about - and when.