Biomarkers in Prostate Cancer

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Disclosure

- Consultant for MDx Health
Objectives

• Acknowledge PSA screening controversy
  » Epidemiology vs personalized health care
  » Cost vs benefit concept
    » Healthcare dollars
    » QOL

• Discuss new tests that seek to improve upon PSA to address patients with significant disease
  » Conventional measures (PSA, Gleason groups) can lead clinicians/patients to treat a substantial number of cases where risks > benefits
  » Distinguish dangerous disease (metastatic or lethal potential) from indolent cases
  » Expense is an important consideration
    » Medicare covers many now
Prostate cancer can be lethal

- Leading solid tumor and 2nd leading cause of death from cancer in American males in 2015

- Lifetime risk of prostate cancer in US:
  - Diagnosis: 1 in 6 men
  - Death: 1 in 33 men
  - 68: Median age at diagnosis
  - 80: Median age at death

Incidence of Metastatic Disease at Presentation 1975-2012 [SEER]

Welch, NEJM, Oct 29, 2015
Mortality rate is decreasing 3.5% per year since 1995 [SEER]
And Yet...
PSA screening is under fire

- US Preventative Services Task Force “D” recommendation
  - Lay press
- Flaws in trials that led to “D”
  - PLCO, ERSPC trials
- Harms > benefit of screening for men as a population ignores the benefit > harm in some
- “C” recommendation would permit shared decision making
- AUA: Screen age 55-69 with shared decision making
- Task force does not reconcile epidemiological trend of CSM and metastatic disease
Improving PSA (Biomarker) Testing

- Age-specific ranges
- Race-specific ranges
- PSA kinetics (velocity, doubling time)
- PSA density
- PSA “derivatives”
  - Free ratio
  - Complexed PSA
  - Intact PSA
  - Precursors [-2]ProPSA
  - PHI
  - 4K

Biomarker tests are evolving rapidly to help address this clinical challenge:

Improve detection of clinically important cancers
Many Prostate Cancer Biomarkers!

Genetic Markers
- Prolaris™
- Decipher™
- OncotypeDx™
- ConfirmMDx®
- ProstaVision™
- GWAS (genome-wide association study)
- SNIPS
- BRCA1&2
- HOX B13

Others
- PCA3
- TMPRSS ERG
- VPAC1
- CTC
- Prostate Core Mitomic Test (PCMT)
- RNA: micro/exosomal/mitochondrial
- Urinary sarcosine
- Promark (tissue staining)
- Circulating DNA
- 4K
- PTEN

J.Urol 2013; 189(2): 422
# Context is Crucial

<table>
<thead>
<tr>
<th>Decision</th>
<th>Tests</th>
</tr>
</thead>
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<td>Who to biopsy</td>
<td>PHI, 4K, Select MDx</td>
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<td>Who to rebiopsy</td>
<td>PCA3, Confirm MDx</td>
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<td>(-) biopsy pts</td>
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<td>Secondary treatment or observation</td>
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<td>postop patients</td>
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# Prostate Cancer Markers

## Test

### Prostate Health Index
- Beckman Coulter
- Blood-based test for patients with a PSA between 2-10 ng/ml (4-10 ng/ml FDA)
- Reduces reduction in prostate cancer risk
- Calculates risk of finding prostate cancer on biopsy
- **Who to Biopsy**

### 4Kscore®
- OPKO
- Indicated for men with an abnormal PSA or DRE as a reflex blood test combined with clinical information to determine an individual patient’s risk for high-grade prostate cancer on biopsy
- For patients who are considering a biopsy or who have had a prior negative biopsy
- Laboratory testing of 4 proteins in the blood (Total PSA, Free PSA, Intact PSA and NKG2) and combined with the patient’s clinical information in an algorithm to predict the individual patient’s risk of having high-grade prostate cancer versus indolent or no cancer
- **Who to Re-Biopsy**

### ConfirmMDx™
- MDxHealth
- Biopsy tissue based test for patients who are repeat biopsy candidates
- Provides risk stratification decision for repeat biopsy
- Eligibility: Patients with a prior negative or HGPIN biopsy result in past 24 months
- Three-gene methylation assay to detect an epigenetic field effect associated with the concentration process at the DNA level

### Progensa® PCA3 Assay
- Hologic Inc.
- Urine-based test, post DRE, which adds useful info when PSA or DRE is inconclusive
- For patients who are considering first or repeat biopsy
- FTA approved for use in conjunction with other patient info to aid in the decision for repeat biopsy in men ≥ 50 years
- **Who to Treat Positive Biopsy**

### Oncotype DX®
- Genomic Health
- Biopsy tissue based test to help determine how aggressive cancer is by providing a likelihood of favorable pathology
- For patients that are NCCN Very Low, Low & Intermediate Risk
- Provides personalized Risk Assessment, aids in the decision for active surveillance or immediate treatment

### ProMark™
- Metmark Genetics
- Biopsy tissue based prognostic assay for patients with prostate Gleason Scores 3+3 and 3+4
- For patients who are deciding between active surveillance and treatment
- Provides a personalized risk score
- Can be used as stand-alone risk score or combined with NCCN risk categories

### ProLaris®
- Myriad Genetics
- Biopsy tissue based test for patients who are Active Surveillance Candidates
- Available post-prostatectomy to determine relative risk of BCR

### Decipher®
- GenomeDX Biosciences
- Tissue based test for patients with adverse pathology post-surgery (radical prostatectomy)
- Provides metastatic risk stratification that can help guide post-operative treatment decisions
- For patients with PCa or positive surgical margins or rising PSA
- Helps determine the need & optimal timing of radiation

### Specimen Provenance
- **Who to Treat Post Surgery**

### Know Error®
- Strand Diagnostics
- Oral swab and biopsy tissue based test provides DNA confirmation of specimen provenance
- Rules out undocumented transportation or contamination of specimen among patients which could lead to misinterpretation of pathology or biomarker
- Increases diagnostic accuracy

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## Science

- FDA approved index of proteins in the blood that combines the concentrations of PSA, freePSA and proPSA in a formula that produces the PHI Score, which has three time the specificity for prostate cancer compared to PSA alone
- Laboratory testing measuring 4 kallikreins in the blood (Total PSA, Free PSA, Intact PSA and NKG2) and combined with the patient’s clinical information in an algorithm to predict the individual patient’s risk of having high-grade prostate cancer versus indolent or no cancer
- Test detects PCA3 gene that is highly specific for prostate cancer
- Measures concentration of prostate cancer gene (PCA3) and prostate specific antigen (PSA) RNA in post-DRE urine and calculates ratio of PCA3 molecules to PSA molecules to produce the PCA3 score
- Test requires 4 tissue sections
- Eight protein signature predicts cancer aggressiveness (>4.5 and or non-organ confined)
- Selected markers eliminate sampling variability, provides a direct analysis of cancerous regions of interest
- Requires 4 tissue sections
- 46-gene expression signature includes cell cycle progression genes selected based upon correlation with prostate tumor cell proliferation
- Polysac score
- Biopsy is < or > than AUA risk group and estimates 10-year mortality risk
- Post-surgical results are similar but provide 10 year risk for BCR
- 23 RNA biomarkers across multiple biological pathways associated with metastasis progression including cell cycle progression, immune system modulation and androgen signaling
- Measures each patient tumor’s metastatic risk based on the whole transcriptome analysis platform
- Decipher provides probability of metastasis at 5 years after surgery, and 3 years after detectable PSA
- Decipher high-risk men may benefit from adjuvant radiation
- Decipher low-risk men can be safely observed with PSA monitoring
- Buccal swab in the clinic sent for DNA match to pathology specimen; may be used with all tissue. STR profiles assessed from multiplex panel of 16 genetic markers
- Results Confirm:
  - DNA Match
  - DNA Non match
  - Contamination

## Results

- PHI results fall into four categories of risk that prostate cancer may be found on biopsy
- 4K results provide percent probability (positive predictive value) of an individual patient’s risk of having high-grade prostate cancer on biopsy
- Three-gene methylation assay to detect an epigenetic field effect associated with the concentration process at the DNA level
- Negative ConfirmMDx results: Avoid repeat biopsy and monitor with routine screening
- Positive ConfirmMDx results: Suspicious areas marked as positive providing repeat biopsy guidance on a prostate map
- As the PCA3 score increases, the likelihood for positive biopsy increases. As the PCA3 score decreases, the likelihood for a positive biopsy decreases
- The greater diagnostic utility occurs at a cutoff score of 25
- Assay looks at 17 genes within 6 pathways (androgen signaling, stromal response, cellular organization, proliferation) to assess tumor aggressiveness
- Genomic Prostate Score (GPS) from 0 to 100
- Likelihood of freedom from high grade and/or non-organ-confined disease
- GPS is reflective of the biology of the tumor at the time of biopsy
- ProMark Score gives a personalized % probability of aggressive cancer
- Interpretation as stand-alone result and in combination with NCCN risk categories
- Results delivered within an easy-to-interpret, personalized report

## Cost

- $499
- **Who to Biopsy**
- Medicare: Currently not covered
- Financial assistance: Available by PCLS
- 866-725-7522 (PCLS) / 865-420-7140 (DC)
- Prostatehealthidx.com
- $1,185
- **Who to Re-Biopsy**
- Medicare: Currently not covered
- Financial assistance: Contact Billing office for issues
- 866-593-7999
- Clinical.opko.com
- $3,300
- **Who to Treat Positive Biopsy**
- Medicare: Covered
-柳本/435368
- Financial assistance: Available for out of pocket expenses
- 866-523-5001
- Pca3.org
- $300-500
- **Who to Treat Post Surgery**
- Medicare: Covered (CPT Code: 81313)
- 800-523-5001
- Pca3.org
- $4,180
- Medicare: Covered
- Financial assistance: Available for out of pocket expenses
- 866-662-6897
- Oncotypeidx.com
- $3,900
- Medicare: Not currently covered
- Financial assistance: Available if out-of-pocket cost are greater than $150
- 877-743-3338
- Metamarkgenetics.com
- $3,400
- Medicare: Covered
- Financial assistance: Available if estimated out-of-pocket costs are greater than $375
- 800-464-7423
- Prolaris.com
- $4,100 cash pay price
- Medicare: Covered
- Financial assistance: Available and patients pay no more than $795 out-of-pocket
- Contact phone number for doctor: 1-800-972-1601
- Genomicdx.com
- $1,780
- Medicare: Currently not covered
- Financial assistance: Available and patients pay no more than $795 out-of-pocket
- 888-924-6779 Ext. 2
- Knowerror.com
Genomic Markers

Context: Screening

What tests exist to better select patients for prostate biopsy?
Can we screen smarter?

PHI
Opko 4K
Select MDx
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PHI: Prostate Health Index

- Precursor forms of PSA elevated in PCa and measurable in serum
- Formula includes tPSA and fPSA, as well as (-2)proPSA
  - Result is % risk of Gleason group 2/3
- Screening pts >50, PSA 2.0-10 and nl DRE gives increased sensitivity/specificity (64/63) compared to PSA
  - Using cutoff of 35, 26% of biopsies could be avoided
  - “3x more likely to diagnose prostate cancer”
  - FDA approved for PSA 2-10
  - Now in NCCN guidelines footnotes as an option
  - Medicare coverage imminent?
  - Cost: <$400

Le, JU, 2010
Lazzeri, BJU, 2013
Catalona, J.Urol 2011
Testing in US clinics

Any cancer

Epstein significant ca

Gleason grp 2/3

n=658
PSA 4-10

Loeb, JUrol, 2015
OPKO 4K Test

- 4 kallikreins: tPSA, fPSA, iPSA, hk2 measured in serum
  - used in nomogram with DRE and age
  - Generates probability score for ≥Gl7/Group 2 prostate cancer
- Tested on serum from ERSCP prostatectomies, good predictor of aggressive disease, then prebiopsy on US patients. Both found AUC 0.82
  - Suggests about half of biopsies could be avoided
  - (this would miss low grade group disease)
- Cost: $400
  - In NCCN footnotes
  - Medicare coverage imminent?

Carlsson, EurUrol, 2013
Voigt, The Prostate, 2013
4K Score Ongoing Evaluation

- **US study:** 1012 men scheduled for prostate biopsy
  - PSA mean approx 5
  - 46% (+) biopsy all grades
  - 23% Group 2/3
  - 4K results examined for cutoffs (reported as % risk)
    - 9% risk cutoff would miss 2.4% of Group 2/3 cancers, but would avoid 43% of biopsies in the cohort

- **European study:** Used Swedish population study with frozen serum since 1986, 1:3 case-control study
  - Test age (40), 50, 60 in 40,000 men with ≥15 yr f/u
  - PSA levels alone separated cases of mets/death but 4K test was significantly better and when applied to the cohort discriminated Grp 2 cases and
    - would avoid biopsy in 38% of men age 60 with PSA ≥3
    - would avoid biopsy in 59% of men age 50 with PSA ≥2
  - **Concl:** If PSA modestly elevated then do 4K to decide on biopsy

Parekh et al., Eur Urol, 2014
Stattin et al., Eur Urol 2015
Select MDx

- Urinary test for Grp 2/3 developed from mRNA profiling
  - HOXC6 and DLX1 levels discriminated Grp 2/3
  - Urine obtained after standardized DRE in men scheduled for PNB
  - n=519 in training cohort (41% + bx, 20% grp 2/3)
  - n=386 in validation cohort (47% + bx, 23% grp 2/3)
    » When combined with DRE, PSAD, FH, hx prior (-) bx: AUC 0.86
      - Sig better than PCA3
    » Approx 50% of the biopsies in the validation group could be avoided
    » Reported as risk score
    » Available in US
      - Cost $300
    » Heralds integration of biomarkers into online risk calculators

Van Nest et al., Eur Urol 2016
Gardiner et al., editorial, Eur Urol 2016
Summary: Screening Smarter

- Use PCPT and/or ERSPC risk calculator
- Use online life expectancy calculator
  » Engage in shared decision-making

- Candidates for clinician consideration
  » Consider molecular tests (PHI, 4K) but watch out for cost
  » Consider MRI but must have an experienced, trained radiologist (cost too)

- *** Minimize infection risk of biopsy
Genomic Markers

Context: Early Detection

If the initial prostate biopsy is negative and concern persists, who to re-biopsy?

PCA3
ConfirmMDX
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Repeat Biopsy: The Numbers

- \( \approx 1.3 \text{M biopsies/yr for screen positive patients} \)
  - Of those, \( \approx 1 \text{M are negative} \)
- 43% repeat biopsy within 3 yr
- Biopsies carry increasing risk in this era of E.coli resistance to antibiotics
  - Infection 8%
  - Hospitalization 4%
- About 50% of Pca identified on repeat biopsy are \( \geq \) Gleason 7
PCA3 for Rebiopsy

- **Urine-based test** done after standardized DRE
- FDA approved for cutoff = 25
- Sens/spec up to 90/50
- Can help guide decision to rebiopsy
- May help avoid up to half of repeat biopsies
- Medicare coverage imminent?

Luo, Asian J Androl, 2014
Confirm MDx Overview

- Indication: For men with a previous negative prostate biopsy and persistent risk factors for Pca
- Assay done on biopsy tissue up to 30 months after biopsy
- Not for ASAP
- DNA-methylation based assay which measures epigenetic changes in key genes associated with carcinogenic events
  - GSTP1 - DNA detoxification
  - APC - apoptosis
  - RASSF1 - cell cycle regulation
- Medicare approved with data development
Epigenetic Changes Influence Gene Expression Without Changing the Genome

- Detects epigenetic field effect associated with the “cancerization” process.

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

- Detection of “halo” extends the coverage of biopsy helping rule in/rule out occult cancers.
Meta Analysis: MATLOC & DOCUMENT

90% NPV for all Pca
96% NPV for clinically significant Pca

ConfirmMDx is the Most Significant Independent Predictor for Prostate Cancer Detection on Repeat Biopsy

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<tr>
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<th>Odds Ratio</th>
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<td>PSA</td>
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<td>Atypia</td>
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N = 803

ConfirmMDx for Prostate Cancer Sample Patient Report

ConfirmMDx Negative
• Avoid repeat biopsy
• Routine screening by PSA & DRE
• Results valid 24-30 months from previous biopsy

ConfirmMDx Positive
• Manage patient as if ASAP pathology result
• Consider performing complete 12 core repeat biopsy
• Obtain additional cores in and around methylated hot spots
Confirm MDx Risk Score

- Level of epi derangements proportional to Gleason group on repeat biopsy

...facilitates shared decision making for repeat biopsy

Van Neste et al., The Prostate, 2016
Genomic Markers

Context: AS vs treatment

If initial prostate biopsy is positive: active surveillance vs treatment?

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Genomic Prostate Score (GPS)*

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

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

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

- PCR-based expression assay
- 17 gene panel
  - 5 reference genes
  - 12 genes covering multiple pathways predictive of:

1. Metastasis & Death when measured in RP specimens
2. Dominant grade pattern 4 & EPE/SV/LN+ when measured in biopsy specimens

* Oncotype DX®, Genomic Health
Gene Selection for the Oncotype DX® GPS Assay

- 727 candidate genes in dominant Gleason samples
  - 374 genes predict outcome (dominant)
- 727 candidate genes in highest Gleason samples
  - 367 genes predict outcome (highest)

288 genes predictive regardless of sampled Gleason pattern

- Consistent performance in biopsies
- Predict PC death, adv. path, BCR
- Value beyond existing measures
  - Represent key pathways
  - Analytical performance

Final 17 GPS Genes

PC, prostate cancer; BCR, biochemical recurrence.
Combining Biologic & Clinical Information Refines Risk Stratification for Individual Patients

NCCN Population-Based Clinical Risk Assessment

- **VERY LOW RISK**: 10% (N=37)
- **LOW RISK**: 49% (N=191)
- **LOW-INTERMEDIATE RISK**: 41% (N=160)

UCSF Validation Study

NCCN Risk Classification

- 10% Very Low-risk
- 49% Low-risk
- 41% Intermediate Risk

GPS Provides Biologic Risk Information

Individuallyized Biologic and Clinical Risk Assessment

- **VERY LOW RISK**: 26% (N=100)
- **LOW RISK**: 31% (N=119)
- **LOW-INTERMEDIATE RISK**: 44% (N=169)

- Gene panel can move individual patients into a different risk category than NCCN would predict
- Population → individual level
- Mentioned in NCCN

Cooperberg et al, AUA 2013
Interpreting the Oncotype DX GPS Report

Interpretation of GPS for this clinical NCCN LOW risk patient:

Likelihood of Favorable Pathology*
84% (95% CI: 76%-89%)

MORE FAVORABLE than by clinical criteria alone. In the expected range of NCCN VERY LOW risk.**

Freedom from High-Grade Disease (dominant Gleason pattern 4 or any pattern 5):
92% (95% CI: 86%-95%)

Freedom from Non-Organ-Confined Disease (pathologic T3 stage):
88% (95% CI: 82%-93%)

*Favorable pathology is defined as freedom from high-grade (dominant pattern 4 or any pattern 5) and/or non-organ confined (pT3) disease.
**Expected ranges for NCCN risk groups were determined from multivariate modeling in the clinical validation study, where 90% of NCCN Very Low risk patients had ≥ 79% chance of favorable pathology and 90% of NCCN Intermediate risk patients had ≤ 67% chance of favorable pathology.

http://www.youtube.com/watch?v=o0XPZQxUBBs
Interpreting the Oncotype DX GPS Report

Interpretation of GPS for this clinical NCCN LOW risk patient:

Likelihood of Favorable Pathology*
65% (95% CI: 54%-74%)

LESS FAVORABLE than by clinical criteria alone.
In the expected range of NCCN INTERMEDIATE risk.**

Freedom from High-Grade Disease (dominant Gleason pattern 4 or any pattern 5):
75% (95% CI: 64%-83%)

Freedom from Non-Organ-Confined Disease (pathologic T3 stage):
72% (95% CI: 61%-80%)

*Favorable pathology is defined as freedom from high-grade (dominant pattern 4 or any pattern 5) and/or non-organ confined (pT3) disease.

**Expected ranges for NCCN risk groups were determined from multivariate modeling in the clinical validation study, where 90% of NCCN Very Low risk patients had ≥79% chance of favorable pathology and 90% of NCCN Intermediate risk patients had ≤67% chance of favorable pathology.

http://www.youtube.com/watch?v=o0XPZQxUBBs
Prolaris®

- Combines RNA expression of cell cycle progression (CCP) genes with standard clinico-pathologic parameters
  - Total 46 genes
  - 31 genes across multiple CCP pathways
  - 15 housekeeper genes

- Each 1 unit change in Prolaris score equals a doubling (or halving) of risk

- Validated on multiple tissue types
  - Biopsy tissue
  - Radical prostatectomy tissue

- Provides personalized risk assessment
  - Prognostic for PCa mortality, metastasis, and BCR
  - Mentioned in NCCN
Prolaris® Adds to Conventional (D’Amico/AUA) Risk Assessment

Also, some AUA intermediate patients have lower risk than AUA low risk patients (AS)

Others have higher risk than AUA high risk patients (37% of PCa death vs. 11% with AUA alone)

3.9% of PCa death vs. 11% with AUA alone (y-axis)

AUA + Prolaris PCa Mortality Risk %
PROLARIS DIFFERENTIATES PROSTATE CANCER SURVIVAL

### Table. 10-Year Death Rate by Polaris Score

<table>
<thead>
<tr>
<th>Polaris Score</th>
<th>10-Year Death Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.0</td>
<td>7</td>
</tr>
<tr>
<td>0.0–1.0</td>
<td>15</td>
</tr>
<tr>
<td>1.1–2.0</td>
<td>36</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>59</td>
</tr>
</tbody>
</table>

Cuzick, AUA 2014 Orlando
Prolaris Biopsy Test Result

ORDERING PHYSICIAN
John Jones MD
320 Walters Way
Salt Lake City, UT 84108

SPECIMEN
Tissue Block
Prostate

Biochip Data:
Accession Date: Jul 20, 2012
Report Date: Aug 16, 2012

PATIENT
Name: James C.
Date of Birth: Feb 2, 1940
Patient ID: 7632
Gender: Male
Accession #: 00927602-0LD

Requisition #: 00927602

Block(s) Analyzed: 2067a

Prolaris Score: -1.1

*Less Aggressive Than Average AUA Low Risk

Interpretation: The Prolaris Score of -1.1 indicates that this cancer is less aggressive than the average cancer in the American Urology Association (AUA) Low Risk category.

AUA Low Risk

-1.1
-1.7
-0.7
0.3
1.3

The above chart illustrates the AUA Low Risk category, which is composed of patients with varying degrees of cancer aggressiveness. Cancer aggressiveness can be stratified within this category based upon Prolaris Scores, which are indicated below the graph.

*US Distribution Percentile: 7%
(For AUA Low Risk)
Interpretation: 7% of patients in the AUA Low Risk category have a lower Prolaris Score.

CLINICO-PATHOLOGIC FEATURES USED FOR ANALYSIS
PSA Prior to This Biopsy: 4.2
Gleason Score: 3+3=6
Clinical T Stage: T1c

10-Year Prostate Cancer-Specific Mortality Risk: 1% (95% CI:0-5%)

Interpretation: The patient has a 10-year mortality risk of 1% if managed conservatively. Mortality risks could be altered by various therapeutic interventions.

Patients with similar clinico-pathologic features, as defined by their CAPRA score, have the same a priori 10-year prostate cancer-specific mortality risk. The addition of the Prolaris Score further differentiates this risk, as illustrated in the above graph, which is specific to this patient's CAPRA score. The orange line depicts the relationship between the Prolaris Score and the mortality risk with the 95% confidence interval indicated by dashed lines and the patient's Prolaris Score indicated by the orange dot.

CLINICO-PATHOLOGIC FEATURES USED FOR ANALYSIS
PSA Prior to This Biopsy: 4.2
Gleason Score: 3+3=6
Clinical T Stage: T1c

Note: Clinico-pathologic parameters are provided by the healthcare provider and have not been verified by Myriad.

Physician and patient names have been changed to ensure confidentiality, but data presented is from actual cases.
ProMark

- Proteomic biomarker panel obtained from prostate biopsy specimens
  - 8 biomarkers predictive of aggressive disease and lethal outcome
  - Like others can discriminate in pts considering AS

- Reports risk score 0-100 (100 is higher risk of unfavorable pathology)
  - Combined with NCCN risk category, refines risk category
Decipher

- Developed for prostatectomy initially
- Now available for biopsies
  - Based on small numbers
- Predicts likelihood of
  - Gleason 4 or 5 in prostatectomy specimen
  - 5-year metastasis risk
  - 10-yr mortality risk

- Covered by Medicare
- Max charge $100 in others

- Not powered sufficiently in biopsy patients

Klein et al., Urology 2016
Summary: Biomarkers in AS Candidates

- **Best data**
  - Oncotype DX
  - Prolaris

- **Cost must be considered**

- **Medicare coverage likely soon**
Genomic Markers

Context: Post Prostatectomy

Additional treatment (e.g. adjuvant RT) following radical prostatectomy?

Decipher

Prolaris
<table>
<thead>
<tr>
<th>Context</th>
<th>Test</th>
<th>Specimen</th>
<th>Indication</th>
<th>Utility</th>
<th>Biomarker</th>
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</thead>
<tbody>
<tr>
<td>Biopsy---- or not?</td>
<td>4K</td>
<td>Serum</td>
<td>Elevated PSA</td>
<td>GS≥7 at bx</td>
<td>RNA PSA and PCA3 PSA isos</td>
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<tr>
<td></td>
<td>PHI</td>
<td>Serum</td>
<td>PSA 2-10</td>
<td>Any GS “ “</td>
<td></td>
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<tr>
<td>Biopsy again---- or not?</td>
<td>PCA3</td>
<td>Urine post DRE</td>
<td>Neg bx</td>
<td>Risk re-bx +</td>
<td>PSA isos</td>
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<tr>
<td></td>
<td>ConfirmMDx</td>
<td>Neg bx tissue</td>
<td>Neg bx</td>
<td>Map poss + re-bx vs -</td>
<td>3 epigen</td>
</tr>
<tr>
<td>Treat---- or not?</td>
<td>Prolaris</td>
<td>Pos bx tissue</td>
<td>NCCN LR/VLR</td>
<td>10 DS mort</td>
<td>46 cell cyc</td>
</tr>
<tr>
<td></td>
<td>OncotypeDX</td>
<td>Pos bx tissue</td>
<td>NCCN LR/VLR</td>
<td>Adv path</td>
<td>17 genes</td>
</tr>
<tr>
<td>More treatment— or not?</td>
<td>Decipher</td>
<td>Prostatectomy tumor tissue</td>
<td>pT2 +SM pT3 BCR</td>
<td>5 yr risk met</td>
<td>22 RNA</td>
</tr>
<tr>
<td>Eval metastatic</td>
<td>CTC</td>
<td>Whole Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Complex post-RP treatment decisions: Should patients have adjuvant XRT?

- Guidelines recommend adjuvant radiotherapy for high-risk post surgery patients
  - pT2 with positive margin
  - Any pT3

- Supported by level 1 evidence from three RCTs

- Demonstrated reductions in:
  - Biochemical recurrence
  - Local recurrence
  - Clinical progression

- However, many men received no benefit from the treatment (SWOG 8794)
  - Control arm - 89% metastasis free survival at 10 years
  - ART arm - more toxicity/side-effects
Decipher genomic signature represents multiple biological pathways involved in aggressive prostate cancer

- Analyzes expression of 22 biomarkers

- Cell Proliferation, Differentiation
  - CAMK2N1
  - MYBPC1
  - PBX1
  - THBS2
  - UBE2C

- Cell Structure, Adhesion, Motility
  - ANO7
  - EPPK1
  - IQGAP3
  - LASP1
  - MYBPC1
  - PCDH7
  - RABGAP1

- Immune System Modulation
  - GLYATL1P4
  - S1PR4
  - TNFRSF19
  - TSBP

- Cell Cycle Progression
  - NFIB
  - NUSAP1
  - ZWILCH

- Androgen-Signaling
  - ANO7
  - PCAT-32
  - UBE2C

Decipher Genomic Classifier

- Probability model (range 0-1) to predict metastasis within 5 years in patients with high risk PCa post prostatectomy

- 22 expressed RNAs from index lesion from RP
- Derived from genome-wide search from cancers of >500 patients (Mayo Clinic Tumor Registry)
  - Covers several oncogenic pathways
    - Cell cycle progression
    - Cell adhesion, motility and migration
    - Immune system modulation
Decipher® developed specifically to predict metastasis

Classifier optimized to discriminate early metastasis (within 5 years) from patients with PSA recurrence only

RP Tumor Registry (Mayo Clinic, 1987-2001)

9,989

PSA recurrence

2,131

Metastasis

213

Metastasis (cases) Within 5 years of PSA recurrence

Abdueva et al., J Mol Diagn 2010, Vergara et al., Front in Gen 2011, Erho et al., J Oncology 2012
Decipher predicts metastasis in pts with biochemical recurrence post RP

Multivariable model:
HR: 1.49 (1.23 – 1.81) for each 0.1 increase in GC score (p<0.001)

More accurate prediction of metastasis risk than clinical risk factors

- Area Under the Curve (AUC) is a combination of sensitivity and specificity
- Decipher outperformed common risk factors
- Clinical risk factors sacrifice specificity for sensitivity
- AUCs <0.70 are not clinically actionable

Predictive power measured by Area Under the Curve (AUC)

- Extraprostatic Extension: 0.65
- Gleason Score: 0.64
- Seminal Vesicle Invasion: 0.59
- Lymph Node Invasion: 0.56
- PreOp PSA: 0.56
- Surgical Margins: 0.49

Simon et al., JNCI 2005
Karnes et al. Journal of Urology 2013
GC predicts those who benefit from adjuvant RT and those who benefit from salvage RT

- For GC high-risk patients, a significant difference (17%) in metastasis was observed at 5 years for the adjuvant (6%) compared to the salvage (23%) ‘arm’ (p=0.008).
- Cox model revealed an 80% reduction in hazards for high GC who received ART compared to SRT.
- Indicates GC high-risk patients may benefit from adjuvant RT over salvage RT.

Den et al JCO 2015
Decipher can help identify which patients benefit from adjuvant treatment to reduce risk of metastasis.

*Source: ASSESS-D and PRO-ACT decision-impact studies
Badani et al., British Journal of Urology Intl 2014; Michaelopolous et al., Cur Med Res Opin 2014
Decipher Post-Operative Report

**Patient Details**

- Patient Name:
- Medical Record Number:
- Date of Birth:
- Date of Prostatectomy:
- Pathology Laboratory:
- Pathologist:
- Address:
- Preoperative PSA (ng/mL):
- Gleason Score:
- SM+  EPE  SVII  LN  BCR  Tertiary Gleason 5

**Clinical Details**

<table>
<thead>
<tr>
<th>Clinical Details</th>
<th>Order Information</th>
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</thead>
<tbody>
<tr>
<td>Preoperative PSA (ng/mL): 4.2</td>
<td>Order Date: 01/02/1945</td>
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<tr>
<td>Gleason Score: 4+3</td>
<td>Specimen Received Date:</td>
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<td>Additional Physician:</td>
<td>Specimen ID:</td>
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<tr>
<td>Address:</td>
<td>Ordering Physician:</td>
</tr>
</tbody>
</table>

**Your Decipher Result – Genomic High Risk**

Decipher Score: 0.7

Risk - Percent Likelihood

- 5-Year Metastasis: 16.4%
- 10-Year Prostate Cancer Specific Mortality: 11.4%

**Interpretation**

Clinical studies concluded that Decipher high risk men with adverse pathology have a poor prognosis overall. These men may benefit from adjuvant or early salvage radiotherapy and consideration for clinical trials. Relevant findings from published clinical studies: Patients with Decipher high risk had 77% 5-year metastases free survival and 70% 10-year cause specific survival. For these patients there was improvement in metastasis free survival favoring adjuvant and early salvage postoperative radiotherapy.

In patients with PSA rise or biochemical recurrence after surgery that received salvage radiotherapy, only 60.5% remained metastasis free after 5 years.

References on reverse

**Your Decipher Result – Genomic Low Risk**

Decipher Score: 0.3

Risk - Percent Likelihood

- 5-Year Metastasis: 1.6%
- 10-Year Prostate Cancer Specific Mortality: 2.5%

**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 >90% 5-year metastases free survival and >90% 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% 2-year metastasis free survival was observed with or without concurrent hormone therapy.

References on reverse
Post RP Biomarkers: Conclusions

- **Decipher**
  - Prognostic of outcome for patients (5yr met, 10yr CSM)
  - If considering post-RP XRT because pathology shows T2SM+, T3, Grp 3:
    - low score, then adj XRT at any PSA level doesn’t affect outcome
      - Salvage only, maybe no ADT
    - high score: adj (PSA undetectable) or salvage at PSA ≤0.2 improves outcomes (BCR and mets rate)
      - Consider additional therapies
  - Medicare covers, others $100 max

- **Prolaris**
  - Predicts 10-yr mortality rate in RP patients
  - Not studied in XRT population but results could affect decisions about XRT
  - Medicare covers for low/very low risk (AS population), others ? $375
Biomarkers: numerous, rapidly evolving
None yet replace initial PSA screening
Only a few will survive as useful biomarkers (cost v. utility)
Technology permits analysis of tiny foci, DNA, RNA, proteins
Consider using tests that correlate with cancer aggressiveness in decision making
  » may decrease “over diagnosis and over treatment” challenges
  » Know context and cost!

Biomarker reimbursement: New Medicare policy 11/14
  » Providers must enroll into CMS Certification and Training Registry for data development