A New Biomarker in Prostate Cancer Care: Oncotype Dx

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Crouse Hospital
Syracuse, NY
Learning Objectives

- Review the current challenges in the prediction and prognosis of prostate cancer
- Review current means for predicting prostate cancer aggressiveness
- Review current available diagnostic tests via genetic signatures
- Understand and interpret the results and clinical relevance of these predictive systems
Clinical Staging Alone Not Adequate for Prognosis

+ DRE (digital rectal exam)
+ PSA (prostate specific antigen)
+ Gleason Score
+ Clinical Stage

≈ 80% predictive diagnostic accuracy
Prostatic Adenocarcinoma

Gleason Grading¹

- Morphologic resemblance to normal prostate
- Degree of invasiveness
- Score = most + 2nd most
- 2005 ISUP²: Grading biopsies:
  - Most + highest remaining grade present
  - Grades 1&2 should not be used
    (most upgraded or found to be benign on RP)
  - Score ranges from 2-10

Screen & Treat
Everybody

Early PSA Era
Screen & Treat Everybody

Don’t Screen and Don’t Treat Anyone

Today

The Challenge and Goal is to Balance:
• Age and health of the patient
• Risk of having aggressive cancer
• Biologic potential of the tumor
• Patient and family desire
Clinical Need in Localized Prostate Cancer

- Over-diagnosis and over-treatment
- Limited confidence in existing risk stratification
- Low-risk disease can be safely managed with AS
- AS under-utilized despite guidelines
Current State of Low Risk Prostate Cancer

Incidenc/Risk\(^1-7\)
- % Newly Diagnosed Low Risk: 46%
- % Lifetime Risk of Progression and Death: 3%

Treatment\(^1-8\)
- % Immediate Treatment: 63%
- % AS/WW: 37%

Surveillance Outcomes: n = 3,762; PCSS 99.4\(^9\)

WW, watchful waiting; AS, active surveillance.

Clear Need and Opportunity to Improve Prostate Cancer Management

- Driver of over treatment is limited accuracy of low risk classification based on measures available today
- Despite low (3%) risk of disease progression and modest treatment benefit, >90% of low risk men receive immediate treatment

“We desperately need the ability to predict which patient has a localized cancer that is going to metastasize and cause suffering and death, and which patient has a cancer that is destined to stay in the patient's prostate for the remainder of his life.”

-American Cancer Society

Treatment Decisions in Prostate Cancer

- Currently urologists use prostate cancer risk to help guide treatment decisions
- What risk group is your cancer?
  - Very low risk
  - Low risk
  - Intermediate risk
  - High risk
What are the Barriers to Adopting Surveillance

- Uncertainties in clinical tools to predict
  - True biologic potential at diagnosis
  - True biologic progression after initiating surveillance (“when to pull the trigger”)
- Anxiety
  - Patient, family, doctors
- Economic/Professional
  - Doctors get trained & paid to treat, not watch
- Legal
  - Failure to diagnose or cure
NCCN Pathway for Very Low Risk CAP

RISK GROUP

Very low
- T1c
- Gleason score ≤ 6
- PSA < 10 ng/mL
- Fewer than 3 prostate biopsy cores positive, ≤ 50% cancer in each core
- PSA density < 0.15 ng/mL/g

EXPECTED PATIENT SURVIVAL

≥ 20 y

INITIAL THERAPY

Active surveillance
- PSA no more often than every 6 mo unless clinically indicated
- DRE no more often than every 12 mo unless clinically indicated
- Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
- EBRT or brachytherapy

≥ 20 y

RAMD prostatectomy (RP)
± pelvic lymph node dissection (PLND)
if predicted probability of lymph node metastasis ≥ 2%

< 10 y

Observation

10-20 y

Active surveillance
- PSA no more often than every 6 mo unless clinically indicated
- DRE no more often than every 12 mo unless clinically indicated
- Repeat prostate biopsy no more often than every 12 mo unless clinically indicated

< 10 y

Active surveillance
- PSA no more often than every 6 mo unless clinically indicated
- DRE no more often than every 12 mo unless clinically indicated
- Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
- EBRT or brachytherapy

Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See Principles of Active Surveillance and Observation (PROS-C).

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NCCN Pathway for Low Risk CAP

RISK GROUP
Low
- T1-T2a
- Gleason score ≤ 6
- PSA < 10 ng/mL

EXPECTED PATIENT SURVIVAL
≥ 10 y
- Active surveillance
  - PSA no more often than every 6 mo unless clinically indicated
  - DRE no more often than every 12 mo unless clinically indicated
  - Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
- EBRT or brachytherapy

< 10 y
- Observation
- RP + PLND if predicted probability of lymph node metastasis ≥ 2%

INITIAL THERAPY

Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See Principles of Active Surveillance and Observation (PROS-C).

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NCCN Pathway for Intermediate Risk CAP

**RECURRENT RISK**
Clinically Localized:

**EXPECTED PATIENT SURVIVAL**

**INITIAL THERAPY**

- Active surveillance:
  - PSA as often as every 6 mo
  - DRE as often as every 12 mo

**ADJUVANT THERAPY**

- Progressive disease:

**RT** (Daily IGRT with IMRT/3D-CRT)
± short-term neoadjuvant/concomitant/adjuvant ADT (4-6 mo)
± brachytherapy

- Undetectable PSA

- Detectable PSA

**Intermediate:**
- T2b-T2c or
- Gleason score 7 or
- PSA 10-20 ng/mL

- RP + PLND if predicted probability of lymph node metastasis ≥2%

- Adverse features:
  - RT or Observation
  - Lymph node metastasis: Observation or ADT or ADT + RT (category 2B)

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INITIAL PROSTATE CANCER DIAGNOSIS

Life expectancy ≤ 5 y and asymptomatic

- DRE
- PSA
- Gleason primary and secondary grade

Life expectancy > 5 y or asymptomatic

Preferred treatment for any therapy is approved clinical trial

INITIAL CLINICAL ASSESSMENT

No further workup or treatment until symptomatic, except in high- or very-high-risk groups

Bone scan if any of these:
- T1 and PSA > 20
- T2 and PSA > 10
- Gleason score ≥ 8
- T3, T4
- Symptomatic Pelvic CT or MRI if any of these:
  - T3, T4
  - T1-T2 and nomogram indicated probability of lymph node involvement > 10%

STAGING WORKUP

Suspicions nodes Consider biopsy

RISK GROUP

Clinically Localized:
- Very low
  - T1c
  - Gleason score ≤ 6
  - PSA < 10 ng/mL
  - Fewer than 3 prostate biopsy cores positive, ≤ 50% cancer in each core
  - PSA density < 0.15 ng/mL/g

- Low
  - T1-T2a
  - Gleason score ≤ 6
  - PSA < 10 ng/mL

- Intermediate
  - T2b-T2c or
  - Gleason score 7 or
  - PSA 10-20 ng/mL

b Men with clinically localized disease could consider use of a tumor-based molecular assay to stratify better risk of adverse pathology at radical prostatectomy or chance of biochemical recurrence or disease-specific mortality after radical prostatectomy.
Ideal Prognostic Test

- Easily obtained specimen
- Accurately stratifies risk by meaningful endpoints
  - Prostate specific survival
  - Recurrence
- Provides significant independent information
- Provides actionable information
Landscape of PCa Genomic Analyses
The Promise of Genomics

Clinical Risk Groups

- Favorable Biology
- Very Low Risk

- Low Risk

- Intermediate Risk

Unfavorable Biology

Intermediate Risk

INDIVIDUAL RISK
The Onco
type 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

• **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

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

**Interpretation of GPS for this clinical NCCN LOW risk patient:**

- **Likelihood of Favorable Pathology**: 84% (95% CI: 76%-89%)
  - More favorable than 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%-98%)
- **Freedom from Non-Organ-Confined Disease** (pathologic T3 stage): 88% (95% CI: 82%-92%)

*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 a 7% chance of favorable pathology and 90% of NCCN Intermediate risk patients had a 6% chance of favorable pathology.*

Patrick Joseph, MD
Laboratory Director
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.
GPS Incorporates Multiple Biologic Pathways Predictive of Prostate Cancer Aggressiveness

The combination of multiple pathways is more predictive than any single pathway.

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

Genes were selected for performance in biopsies and prediction of PC death, adverse pathology, and BCR.

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.
### Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Mean Range</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at Diagnosis</strong></td>
<td></td>
<td>58.3 years</td>
<td>38-77</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td>359 (91%)</td>
<td>13 (3%)</td>
<td>23 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>PSA</strong></td>
<td></td>
<td>83 (21%)</td>
<td>262 (66%)</td>
<td>50 (13%)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical T-stage</strong></td>
<td></td>
<td>228 (58%)</td>
<td>118 (30%)</td>
<td>49 (12%)</td>
<td></td>
</tr>
<tr>
<td><strong>Central Biopsy</strong></td>
<td></td>
<td>301 (76%)</td>
<td>94 (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
<td></td>
<td>High Grade</td>
<td>High Grade and/or pT3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endpoint Grade/Stage at RP</strong></td>
<td></td>
<td>70 (18%)</td>
<td>87 (22%)</td>
<td>123 (31%)</td>
<td></td>
</tr>
</tbody>
</table>

## Interpretation of Genomic Prostate Score

<table>
<thead>
<tr>
<th>NCCN Risk Group</th>
<th>Likelihood of Favorable Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>80%</td>
</tr>
<tr>
<td>Low</td>
<td>70%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>60%</td>
</tr>
</tbody>
</table>

*Tosoian et al, J Urol 190:1218, 2013*
Successful Validation of GPS: Improved Risk Discrimination with Addition of GPS to NCCN

![Graph showing the likelihood of favorable pathology (%)]

- **NCCN Very Low** = 84%
- **NCCN Low** = 75%
- **NCCN Low-Intermediate** = 56%
- **Very Low**
- **Low**
- **Low-Intermediate**

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

Cooperberg et al, AUA 2013
Combining Biologic & Clinical Information Refines Risk Stratification for Individual Patients

Population-Based Clinical Risk Assessment

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

GPS Provides Biologic Risk Information

- **VERY LOW RISK**: GPS=8, 84%
- **LOW RISK**: GPS=25, 75%
- **LOW-INTERMEDIATE RISK**: GPS=51, 57%

UCSF Validation Study NCCN Risk Classification

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

GPS

- Adds more accurate risk assessment by combining biological and clinical risk factors
- Predicted which patients have risk consistent with their NCCN clinical risk group
- 35% of men in the NCCN Low-risk group had more indolent biology and likelihood of favorable pathology consistent with Very Low-risk
- 10% of men in the NCCN Low-risk group had more aggressive biology and likelihood of favorable pathology consistent with Intermediate risk
- Identified patients in the NCCN Very Low-risk group who had more aggressive biology, with likelihood of favorable pathology consistent with Low and Intermediate risk disease
- Identified patients with Intermediate risk who had more indolent biology, predicted to be consistent with Low risk disease
- Enables more accurate identification of a larger population of patients who can more confidently choose active surveillance
- Precisely identifies a patient’s tumor biology and refines the population-based clinical risk assessment with a more personalized risk assessment

Cooperberg et al, AUA 2013
# CPDR Validation Study Clinical Characteristics Representative of a Contemporary Patient Population

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

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

GPS Predicts AP and BCR Across Different Racial Groups

Tumor aggressiveness, as measured by GPS, was similar between races

GPS was predictive of outcome in both Caucasian and African-American men

<table>
<thead>
<tr>
<th>Event</th>
<th>Race</th>
<th>Variable</th>
<th>N</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Pathology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>GPS per 20 units</td>
<td>288</td>
<td>4</td>
<td>4.05</td>
<td>(2.57-6.60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>African-American</td>
<td>GPS per 20 units</td>
<td>79</td>
<td>2.86</td>
<td>(1.18-7.61)</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td><strong>Event</strong></td>
<td>Race</td>
<td>Variable</td>
<td>N</td>
<td>HR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>BCR</td>
<td>Caucasian</td>
<td>GPS per 20 units</td>
<td>305</td>
<td>2.97</td>
<td>(2.00, 4.33)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>African-American</td>
<td>GPS per 20 units</td>
<td>82</td>
<td>3.50</td>
<td>(1.02, 11.74)</td>
<td>0.046</td>
<td></td>
</tr>
</tbody>
</table>

Validation Studies

- Adds independent predictive information beyond standard clinical and pathological measures
- Predicted multiple clinically relevant endpoints (AP, BCR)
- Tumor aggressiveness was similar between white and black men
Clinical Utility Study #1: Confidence and Utility

In 85% of patients, physicians indicated increased confidence in their treatment recommendations.

In 78% of patients, physicians found the GPS useful in making treatment recommendations.

Badani et al, SUO 2014
**Oncotype DX Genomic Prostate Score (GPS)** uses RT-PCR to determine the expression of 17 genes in tumor tissue. GPS is calculated from the gene expression results and ranges from 0 to 100.

**Clinical experience** with GPS is based on a prospectively-designed validation study of biopsy tissue from 388 patients with localized prostate cancer meeting NCCN® Very Low, Low, and Intermediate risk criteria.\(^1^2\) The interpretation on this page is specific for a patient with the indicated GPS and NCCN Low risk criteria, which includes all of the following: Gleason Score ≤ 6, PSA < 10 ng/ml, and clinical stage T1-T2a.

**Interpretation of GPS for this clinical NCCN LOW risk patient:**

![Graph showing the likelihood of favorable pathology](image)

**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%)
59 year-old patient
PSA: **5.2**
Gleason Score: **3+3=6**
Number of cores positive/collected: **3/12**
>50% tumor involvement in any core: **No**
Stage: **T1c**
PSA Density: **0.13**
Life Expectancy: **25 yrs.**

Initial Clinical Risk (NCCN): **Low**

Pre GPS Recommendation: **Undecided**

**GPS RESULTS**

GPS of **10: NCCN Very Low**
Likelihood of favorable pathology: **83%**

Post GPS Recommendation: **AS** and patient agreed.
General Conclusions

• Current tests harness the power of biology and genomics to provide a more precise and accurate assessment of risk based on individual tumor biology.

• Validated in large studies and can be used along with established clinical and pathological parameters to define prediction and prognosis of PCa behavior for each patient.

• Further collection of data and introducing new assays to search different pathways and signatures of individual cancers may lead to significant breakthrough in personalized oncology approach.
Active Surveillance v. 2.0

**Current Paradigm**
- **Initial Bx & Risk Categorization**
  - Comorbidity & Life Expectancy
  - Patient desire
- Re-biopsy to improve accuracy of risk classification
- Periodic re-evaluation for change in risk categorization
- Intervention
  - Change in risk categorization
  - Worry over PSA
  - Patient desire

**Genomic Based Paradigm**
- No change
- Reduce burden of determining eligibility
  - Substitute a biomarker for a 2nd biopsy
- Improve patient selection
  - Favorable score: Increase confidence that AS is safe
  - Unfavorable score: Increase acceptance that RX is warranted
- Change intensity of monitoring
  - Favorable score → Less intense
  - Unfavorable score → More intense
- Serial biologic monitoring
- Help decide when to “pull the trigger” for RX
"I’d better run some tests... It could be cancer."