Prostate Cancer Genetic Testing
How to Hedge Bets in Selecting Patients for Surveillance

Michael Brooks, MD
Assistant Professor
Metastasis and PCSM in active surveillance cohorts

- **Toronto Cohort - 993 men**
  - 2.8% developed metastatic disease, only 2/28 patients were not upgraded to Gl ≥ 7 prior to clinical metastasis
  - 1.5% died from prostate cancer
  - 55% 15-yr TFS

- **Johns Hopkins Cohort – 1298 men**
  - 5 patients developed metastatic disease
  - 2 prostate cancer deaths
  - 37% 15-year TFS

- **GAP-3 – 15,101 men**
  - 45 patients developed metastasis, 21 w Gl > 6 prior to development
  - 17 prostate cancer deaths, 7 w Gl > 6
  - 27% converted to treatment

- **PRIAS – 5302 men**
  - 8 patients with metastatic disease
  - 1 prostate cancer death
  - 25% 15-year TFS

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GAP-3 Cohort –
Largest Active Surveillance Cohort in the World

• 25 established cohorts (USA, Canada, Australia, UK, and other European Countries)
• 15,101 Patients
• Median Follow-Up 2.16 years (IQR 1.02-4.47 years)
• Maximum Follow-Up 21.3 years

Bruinsma SM, et al. BJU Int 2018; 121:737-744
GAP-3 Cohort – Largest Active Surveillance Cohort in the World

• 5625 Patients (37%) Discontinued AS
  • 46.2% Progression per Protocol
  • 9.1% due to Patient/Physician Anxiety
  • 7% Death (mostly from other-cause)
  • Only 3.3% switched to WW

• Similar to other reported cohorts
  • 10 year treatment-free survival 47-63.5%
  • 10 year cancer-specific survival 98-100%

Bruinsma SM, et al. BJU Int 2018; 121:737-744
Risk of Adverse Pathology

- Clinical Low-Risk Prostate Cancer
  - 42-49% risk of GS >6 on RP
  - 9-16% risk Non-Organ Confined Disease

- Clinical Very Low-Risk Prostate Cancer
  - 31-34% risk of GS >6 on RP
  - 8-23% risk Non-Organ Confined Disease

Carlsson S, et al. BJU Int 2016; 118:205-12
Adverse Pathology → Long-Term Oncologic Outcomes

• Extraprostatic Extension
  • 4.5x the risk of distant metastasis
  • 5x the risk of death from prostate cancer

• Primary Gleason Grade 4 or greater
  • 3-9x the risk of distant metastasis
  • 5-10x the risk of death from prostate cancer

Table 3. Univariate and Multivariate Cox Regression Analyses of Histopathological Risk Factors Based on Tumor Specimens from Radical Prostatectomy.

<table>
<thead>
<tr>
<th>End Point and Risk Factor</th>
<th>No. of Men</th>
<th>No. of Events</th>
<th>Relative Risk with Adjustment for Age Group (95% CI)*</th>
<th>Relative Risk with Adjustment for Age Group and Additional Factors (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distant metastasis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Margins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>184</td>
<td>29</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Positive</td>
<td>99</td>
<td>32</td>
<td>2.73 (1.63–4.37)</td>
<td>1.26 (0.73–2.20)</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>151</td>
<td>13</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Present</td>
<td>112</td>
<td>47</td>
<td>6.59 (3.54–12.27)</td>
<td>4.50 (2.34–8.64)</td>
</tr>
<tr>
<td><strong>Gleason score of prostatectomy specimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–6</td>
<td>88</td>
<td>4</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>7</td>
<td>157</td>
<td>37</td>
<td>6.27 (2.23–17.59)</td>
<td>3.10 (1.05–9.11)</td>
</tr>
<tr>
<td>8 or 9</td>
<td>18</td>
<td>20</td>
<td>17.82 (6.08–52.28)</td>
<td>9.44 (3.09–28.84)</td>
</tr>
<tr>
<td><strong>Death from prostate cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Margins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>184</td>
<td>24</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Positive</td>
<td>99</td>
<td>24</td>
<td>2.55 (1.42–4.56)</td>
<td>1.16 (0.62–2.17)</td>
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<tr>
<td>Extracapsular extension</td>
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<td></td>
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<tr>
<td>Absent</td>
<td>151</td>
<td>9</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Present</td>
<td>112</td>
<td>38</td>
<td>7.61 (3.66–15.84)</td>
<td>5.21 (2.42–11.22)</td>
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<tr>
<td><strong>Gleason score of prostatectomy specimen</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>87</td>
<td>5</td>
<td>1.91 (0.46–7.99)</td>
<td>0.99 (0.23–4.33)</td>
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<tr>
<td>4–5</td>
<td>70</td>
<td>21</td>
<td>11.78 (3.51–39.55)</td>
<td>5.73 (1.59–20.67)</td>
</tr>
<tr>
<td>8 or 9</td>
<td>38</td>
<td>19</td>
<td>20.06 (5.93–67.91)</td>
<td>10.63 (3.03–37.30)</td>
</tr>
</tbody>
</table>

* The model was adjusted for age group (<65 vs. ≥65 years).
† The model was adjusted for age group (<65 vs. ≥65 years), PSA level, margins, capsular extension, and Gleason score.

Adverse Pathology → Long-Term Oncologic Outcomes

- Nomograms Utilize Grade and Stage to Predict Prostate Cancer Mortality
- Surgical Margin Status, PSA Doubling Time are less informative
- AUC 0.79 – 0.82
- Active Surveillance increasing among men < 55 years of age, necessitating improved long-term risk predictions
  - 2010 – 8.61%
  - 2015 – 34.6%

How do we use today’s tools to improve accurate risk assessment?

Goals:
1. Treat patients who are at risk
2. Avoid treatment in patients who are safe to survey
Two problems, Two solutions -

**Under Sampling**

**Under Grading / Staging**

https://www.gehealthcare.com/products/magnetic-resonance-imaging/3-0t/signa-pioneer

https://www.ustoo.org/genetics-and-genomic-testing
Two problems, Two solutions -

Under Sampling

https://www.gehealthcare.com/products/magnetic-resonance-imaging/3-0t/signa-pioneer
https://www.ustoo.org/genetics-and-genomic-testing
MRI improves biopsy accuracy – less likely to miss the index lesion

NCI Cohort Study – 1003 men w MR/US fusion bx and TRUS bx

- Targeted biopsy dx 30% more high-risk cancers (173 vs 122)
- Adding TRUS Bx to Targeted Bx led to 103 more cases of cancer (83% low risk, 5% high risk)
- 170 patients underwent RP – compared to whole mount path, Targeted MR/US biopsy – 77% (67-84%) sensitive, NPV 70% (58-80) for Intermediate to High-risk disease (For standard biopsy alone – both 53%).
MRI improves biopsy accuracy – less likely to miss the index lesion

**Large Prospective Biopsy-Naïve Trials -**

- **PROMIS Trial** – identification on MP-MRI compared to Template Mapping biopsy and TRUS Bx
  - MP-MRI Sensitivity for clinically significant PCa – 93% (95% CI 88-96%), NPV 89% (83-94%)
  - Sensitivity MP-MRI compared to standard TRUS Bx - 93% vs 48%
  - 418/576 Men had + MRI, PPV 51%
  - Assumes targeted MP-MRI biopsy would achieve similar diagnostic accuracy as TPM

- **PRECISION Trial** – randomized: MRI w or wo targeted biopsy vs TRUS Bx (noninferiority study)
  - Clinically significant prostate cancer dx in 38% men in MRI-targeted biopsy group vs 26% in the TRUS Bx group
  - Fewer men diagnosed w insignificant cancer in MRI arm than TRUS Bx (9% vs 22%)
  - Minimal follow up for those who did not undergo biopsy

MRI improves biopsy accuracy – less likely to miss the index lesion

Performance in AS cohorts -

- UCSF AS Cohort Study - 207 men with MRI Guided Biopsies
  - Upgrade detected in 14% of cohort based on MRI fusion bx alone
  - Fusion biopsy detected an additional 34 Gl ≥3+4 cancers not detected on systematic bx. But, missed 39 Gl ≥3+4 cancers when used alone.
  - 9% of Gl ≥4+3 would be missed with fusion alone

- AS MRI Study (ASIST) – multicenter prospective trial: Systematic Bx vs MRI Fusion + systematic – 273 patients
  - 14% men in MRI arm upgraded to ≥GG2 on fusion bx alone
  - No difference in GG1 men upgraded to GG2

- NCI AS Cohort – 542 AS Patients underwent Confirmatory MP MRI Fusion biopsy
  - 20.5% with negative confirmatory bx
  - Median PFS for patients who continued AS with negative or positive confirmatory bx was 44.6 and 74.3 months, respectively (p<0.01)

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Genomic Testing

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https://www.ustoo.org/genetics-and-genomic-testing
# Genomic Testing To Improve Risk Prognostication

## Commercially Available Genomic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Biopsy Specimen?</th>
<th>Validated in AS?</th>
<th>Validated Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decipher Genomic Classifier</strong></td>
<td>22 markers – cell differentiation, proliferation, adhesion, motility, structure, cell-cycle progression, mitosis, immune regulation GCS range 0 to 1</td>
<td>Yes</td>
<td>Yes</td>
<td>High Grade Disease Metastasis after RP or RT PCSM</td>
</tr>
<tr>
<td><strong>Prolaris Cell Cycle Progression</strong></td>
<td>31-cell cycle related genes, 15 house-keeping genes CCP scale -3 to 7 CCR – combination of CAPRA, CCP</td>
<td>Yes</td>
<td>Yes</td>
<td>10-yr mortality w/o treatment Recurrence after RT or RP Metastasis after RP</td>
</tr>
<tr>
<td><strong>Oncotype DX Genomic Prostate Score</strong></td>
<td>17 genes, 12 cancer-related genes – four biologic pathways: androgen signaling, stromal response, cellular organization, proliferation GPS range 0 to 100</td>
<td>Yes</td>
<td>Yes</td>
<td>Adverse pathology at RP Recurrence and Metastasis after RP PCSM after RP</td>
</tr>
</tbody>
</table>
Decipher – Genomic Classifier

Validation and Interpretation

• Validated in Biopsy Specimen to predict Recurrence, Metastasis and Prostate Cancer Death after RP or RT
  • 5-yr risk of metastasis for GC Score Low risk (<0.45) 4.1%, intermediate (0.45-0.60) 7.8%, and high risk (>0.60) 21%
  • 5-yr risk of PCSM – low 0%, intermediate 0%, high 9.4%
• GC Score can be combined w NCCN risk group to improve prognostic accuracy
• In an AS cohort, GC score is independent of MRI PIRADS designation in predicting upgrading
  • 102 NCCN Low and intermediate risk patients
  • Higher GC correlated with GG2 (vs GG1) on fusion biopsy, whereas PIRADS did not
  • 14 patients underwent RP, 5 with AP, where 4/5 were designated high risk by GC score

Prolaris – Cell-Cycle Progression

Validation and Interpretation

- Developed using two cohorts, RP and TURP
  - For each unit CCP increase, the Hazard Ratios for PCSM were 1.74 and 2.57, respectively
- Validated in biopsy specimen as an independent predictor of PCSM with conservative management and as a combined Clinical Cell Cycle Risk Score (CCR)
  - CCR is a linear combination of CAPRA and CCP
  - CCR = 0.39 x CAPRA + 0.57 x CCP
- CCR recently validated in a conservatively managed cohort of men with low and favorable-intermediate risk disease
  - CCR = 0.8 represents the 90th percentile
  - No deaths observed below the threshold

Lin DW, et al. Uro Onc Seminars 2018; 36
OncotypeDx – Genomic Prostate Score

Validation and Interpretation

• Initial validation in clinical low and intermediate risk cohort
  • Each 20-point increase independently associated with increased odds of high grade disease (OR 2.3), and non-organ confined disease (OR1.9)

• Independent Validation in Large U.S. Healthcare System – Median Follow-up 9.8 years
  • No Metastasis or Prostate Cancer Deaths observed in NCCN low or intermediate risk patients with GPS < 20
  • 5-year risk of metastasis for Intermediate risk patients with GPS > 40 similar to high risk patients (16 vs 15%)

• Validated in men on AS who underwent delayed RP
  • Each 5-point increase independently associated w increased risk of AP HR 1.16-1.29, and BCR (HR 1.10, 95% CI 1.00-1.21)
  • Serial GPS on AS remain stable
  • After accounting for PSA density, Age, percent positive cores, GPS improves prediction of biopsy upgrading, while PIRADS did not
  • GPS < 16 (<25th percentile) had a 74% NPV for biopsy upgrading 3 years after testing

Active Surveillance Pathway

- Incorporate both MRI and Genomic Testing
- Use all available staging and grading data to inform patient of risk
- Consider the patient’s health preferences when making an informed decision

Fine ND, et al. BJU Int 2019
CASE PRESENTATION
Case Overview

69 year old healthy male with a history of both BPH with moderate LUTS, managed with tamsulosin, and very-low risk prostate cancer managed on active surveillance for 3 years, now with a rising PSA

Presents to clinic for a second opinion

PSA (ng/mL)

<table>
<thead>
<tr>
<th>Date</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/07/2018</td>
<td>10.97</td>
</tr>
<tr>
<td>09/20/2017</td>
<td>8.23</td>
</tr>
<tr>
<td>12/08/2016</td>
<td>7.76</td>
</tr>
</tbody>
</table>
Case Overview

69 year old healthy male with a history of both BPH with moderate LUTS, managed with tamsulosin, and very-low risk prostate cancer managed on active surveillance for 3 years, now with a rising PSA

On further chart review, his last biopsy was negative other than one suspicious core at the left apex.

**12/01/2017 PATHOLOGY:**
1. Prostate, right base, biopsy (A) - Focal high grade prostatic intraepithelial neoplasia.
2. Prostate, right mid, biopsy (B) - Benign prostatic tissue.
3. Prostate, right apex, biopsy (C) - Benign prostatic tissue.
4. Prostate, left base, biopsy (D) - Benign prostatic tissue.
5. Prostate, left mid, biopsy (E) - Focal high grade prostatic intraepithelial neoplasia.
6. Prostate, left apex, biopsy (F) - Rare atypical glands, highly suspicious for focal adenocarcinoma
Case Overview

69 year old healthy male with a history of both BPH with moderate LUTS, managed with tamsulosin, and very-low risk prostate cancer managed on active surveillance for 3 years, now with a rising PSA.

His physical exam is significant for an enlarged prostate on DRE approximately 60g, but no nodules.
Case Overview

69 year old healthy male with a history of both BPH with moderate LUTS, managed with tamsulosin, and very-low risk prostate cancer managed on active surveillance for 3 years, now with a rising PSA – 10.97, DRE 60g, no nodules

NEXT STEP?
A. Repeat PSA in 6-12 months
B. MP-MRI
C. Repeat Standard Biopsy
D. Immediate treatment
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MRI (12/11/2018):

IMPRESSION:

Approximately 1.4 cm midline base anterior transition zone lesions with imaging features suspicious for clinically significant prostate cancer (PI RADS 4).

No lymphadenopathy.

Transition zone hypertrophy with distended urinary bladder.
Case Overview

69 year old healthy male with a history of both BPH with moderate LUTS, managed with tamsulosin, and very-low risk prostate cancer managed on active surveillance for 3 years, now with a rising PSA – 10.97, DRE 60g, no nodules

FINAL DIAGNOSIS

Targeted prostate, biopsies - Adenocarcinoma of the prostate, Gleason score 3+3=6, grade group 1 involving three of four cores (25%, 3 mm, 35%, 3 mm, 10%, 1 mm).

Prostate Cancer Biopsy Summary

Number of cores examined: 4
Number of cores positive: 3
Highest Grade Group: 1
Highest % of core involvement: 35%
Cribriform pattern 4: Absent
Intraductal carcinoma: Absent
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69 year old healthy male with a history of both BPH with moderate LUTS, managed with tamsulosin, and very-low risk prostate cancer managed on active surveillance for 3 years, now with a rising PSA – 10.97, Gl 3+3 in 3/4 Cores, up to 35%
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69 year old healthy male with a history of both BPH with moderate LUTS, managed with tamsulosin, and very-low risk prostate cancer managed on active surveillance for 3 years, now with a rising PSA – 10.97, Gl 3+3 in 3/4 Cores, up to 35%

Decipher Low Risk

Patient elected continued active surveillance