Prostate Cancer Genomics – When To Treat and With What?

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Relevant Disclosures

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• Unrestricted grant support – Metamark Genetics
• Collaborative research – Myriad Genetics
Genomics Will Transform Our Ability to Understand Malignancies

- 1817
- 1917
- 2017
Clinically Available Genomics in Prostate Cancer: Where are we Now

Multiplexed RT-PCR Assays FFPE

**Prolaris**: CCP

**PROLARIS**: cell cycle progression (CCP) Score
ratio of 31 proliferation genes to 15 normal genes

**OncotypeDx Prostate (GPS)**

- Stromal Response Group Score: SFRP4, BGN, COL1A1
- Androgen Signaling Group Score: KLK2, SRD5A2, FAM13C1, AZGP1
- Cellular Organization Group Score: GSN, GSTM2, TPM2, FLNC
- Proliferation: TPX2
- 12 Genes / 5 Controls

**Decipher**

- 1.4 million probes
- Genome Wide (coding and non coding RNAs)
- Reports on 22 RNAs
Use of Genomic Testing is Growing

Use of Genomics in Prostate Cancer nearly doubled from 2015 to 2016

Total no. patients tested

<table>
<thead>
<tr>
<th>Year</th>
<th># patients tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>23,899</td>
</tr>
<tr>
<td>2016</td>
<td>39,401</td>
</tr>
</tbody>
</table>
Current use is to better determine prognostic risk.
Next steps are to predict therapeutic response.
When To Treat?

Genomics for Men of Favorable Risk (NCCN VLR, LR, Favorable Intermediate)
Active Surveillance and Favorable Risk Prostate Cancer

- Active surveillance (serial biopsy, serum tests, exam, +/-imaging) is a valid treatment strategy for favorable risk men
  - Relatively few men with very low or low risk prostate cancer will progress to die of their disease if immediate local therapy is deferred (Bill-Axelson et al. NEJM 2014, Hamdy et al. NEJM 2016, Tosoian et al JCO 2015)

- Active surveillance should be considered in very-low, low risk men and some favorable intermediate risk men
  - Rates of progression are higher as clinical risk increases
  - Imaging / Genomic Testing can be considered to qualify candidates

Cooperberg et al JAMA 2015
Very Low Risk men – Active Surveillance is Standard

Choice of Surveillance
- Increases mortality by 1.8 months while increasing treatment free interval by 6.4 years (Xia et al CCR 2012)

Serial PSAs, DRE, biopsy
Genomics will likely play a marginal role
- Exception for understudied populations
  - Young, AAM, +FamHx

Jeffrey J. Tosoian et al. JCO 2015;33:3379-3385
Low risk prostate cancer is ~2.5x as likely to be reclassified to intermediate risk

11% reduction in rate of metastasis if treated in SPCG-4 (reduction in PCSM not significant) (Bill-Axelson NEJM 2014)

~2.5x increased risk of metastasis at 10 years in ProtecT if initial treatment deferred with many more progressing to incurable disease (Hamdy NEJM 2016)

Low risk AS patients are NOT indicative of low risk patients (8% ≥ 4 cores for AS, 49% ≥ 4 cores for RP) (Tosoian et al submitted)

Can we use Genomics to better select LR/F-IR men for AS?
Does GG1 disease have metastatic potential?
Genomic markers of aggressive disease in Gleason Pattern 3 tissue from Prostatectomy specimens: PTEN loss, 8p/LPL loss, 8q/MYC gain

Sampling of **Gleason pattern 3 (G3)** tissue from prostatectomy specimens harboring:
- GS 3+3=6
- GS 3+4=7
- GS 4+3=7

Evaluation of:
- PTEN loss by IHC
- PTEN deletion by FISH
- LPL/8p loss by FISH
- MYC/8q gain by FISH

Trock et al, Mod Path 2016
Genomic classifier for aggressive disease (Decipher metastasis scores) are elevated in a small but not insignificant proportion of pure GG1 tumors.

Tissue obtained from prostatectomy specimens with only GG1 disease:
43 (13%) had intermediate risk genomic classifier score
25 (7%) had high risk genomic classifier score

Klein et al, J Urol 2016
Genomic patterns of high risk disease cluster together and are found in ~7% of Favorable Risk Patients

- 7% of the UCSF cohort clustered with higher risk patients from GRID, 4th quartile, of AGR score of 18 prognostic pathways (Cooperberg AUA 2017)
- High GPS scores were found in 7% of active surveillance candidates and these men had a higher risk of progression after treatment (Klein et al. Eur Urol 2014).
- CCP scores >1 found in 8% of favorable risk men (Tosoian et al BJUI 2017)
Current Strategies for AS Qualification

NCCN VLR

No Routine

Additional Testing

Active Surveillance

*AAM, men with +FamHx, Young men are understudied

NCCN LR or Favorable IR

Considering AS

mpMRI/Fusion Biopsy at 3mo

GG1 or GG2

Genomics

> GG3

Active Surveillance

Treatment

Low

Ave

Hi

1.4 million probes
Genome Wide (coding and non coding RNAs)

Prolaris: CCP

OncotypeDx Prostate (GPS)

Decipher

PROLRARIS: cell cycle progression (CCP) Score

ratio of 31 proliferation genes to 15 normal genes

12 Genes / 5 Controls
What to Treat With?

Genomics for Men Prioritized to Treatment (NCCN UF-I, HR, VHR)
Intermediate Risk Prostate Cancer – Multiple Treatment Options

- Multiple treatment options, large variance of risk
- For men undergoing radiation based therapy ADT improves progression free survival even with dose escalation (Bolla et al JCO 2016)
- For men undergoing radiation based therapy brachy-boost can improve local control (Morris et al IJROBP 2016)
- For men with <20 years LE, oncological control for RP vs RT based approaches appear similar with RP having higher short term morbidity
- Subtotal gland therapies being investigated / utilized
### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>UVA</th>
<th></th>
<th>MVA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI) p-value</td>
<td></td>
<td>Hazard Ratio (95% CI) p-value</td>
<td></td>
</tr>
<tr>
<td>Biopsy Grade Group 1-2</td>
<td>Reference</td>
<td>1</td>
<td>Reference</td>
<td>1</td>
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<tr>
<td>Biopsy Grade Group 3</td>
<td>1.7 (0.6 – 5.3)</td>
<td>0.326</td>
<td>0.9 (0.3 – 3.2)</td>
<td>0.923</td>
</tr>
<tr>
<td>Log 2 PSA at First Line Treatment</td>
<td>0.8 (0.5 – 1.4)</td>
<td>0.368</td>
<td>1.2 (0.6 – 2.7)</td>
<td>0.546</td>
</tr>
<tr>
<td>Age at First line Treatment</td>
<td>1.1 (1.0 – 1.2)</td>
<td>0.012</td>
<td>1.1 (1.0 – 1.2)</td>
<td>0.065</td>
</tr>
<tr>
<td>Decipher Biopsy*</td>
<td><strong>1.6 (1.2 – 2.1)</strong></td>
<td><strong>0.001</strong></td>
<td><strong>1.5 (1.1 -2.1)</strong></td>
<td><strong>0.009</strong></td>
</tr>
</tbody>
</table>
How Physicians Can Use Genomics (Decipher) in the Unfavorable Intermediate (UF-I) Setting

- Genomics may also be able to guide staging in UF-I risk men, use of advanced imaging and treatment intensification in HR/VHR men

- **Extended template pelvic node dissection**
- Hypofractionation can be considered
- Length of ADT can be adjusted based on risk

NCCN UF-I

Considering Treatment

Decipher

Biopsy

EBRT*+ADT

EBRT*+ADT *
  +Brachy

RP+ePLND*

RP+PLND

Brachy

EBRT*

Subtotal/focal

TX UROLOGY SPECIALISTS
When to Treat with Adjuvant RT?
Genomics for Men with Adverse Pathological Features at RP
Meta-analysis of 855 patients from five cohorts shows Decipher is a significant predictor of metastasis across all clinical subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>730</td>
<td>1.46 (1.3-1.64)</td>
<td>&lt;0.001</td>
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<tr>
<td>African-American</td>
<td>106</td>
<td>1.43 (0.95-2.15)</td>
<td>0.087</td>
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<tr>
<td>Preoperative PSA (ng/mL)</td>
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<td></td>
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<tr>
<td>&lt;5</td>
<td>457</td>
<td>1.91 (1.29-2.55)</td>
<td>0.001</td>
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<tr>
<td>5-10</td>
<td>277</td>
<td>1.42 (1.19-1.7)</td>
<td>&lt;0.001</td>
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<tr>
<td>&gt;10</td>
<td>457</td>
<td>1.47 (1.25-1.72)</td>
<td>&lt;0.001</td>
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<tr>
<td>RP Gleason Score</td>
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<tr>
<td>≤5+4</td>
<td>459</td>
<td>1.43 (1.1-1.85)</td>
<td>0.007</td>
</tr>
<tr>
<td>4+3</td>
<td>171</td>
<td>1.48 (1.15-1.96)</td>
<td>0.002</td>
</tr>
<tr>
<td>≥8</td>
<td>222</td>
<td>1.24 (1.06-1.45)</td>
<td>0.008</td>
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<tr>
<td>Surgical Margins</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>356</td>
<td>1.45 (1.21-1.73)</td>
<td>&lt;0.001</td>
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<tr>
<td>Positive</td>
<td>499</td>
<td>1.44 (1.25-1.66)</td>
<td>&lt;0.001</td>
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<tr>
<td>Extraprostatic Extension</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Absent</td>
<td>492</td>
<td>1.44 (1.16-1.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>Present</td>
<td>359</td>
<td>1.42 (1.24-1.63)</td>
<td>&lt;0.001</td>
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<tr>
<td>Seminal Vesicle Invasion</td>
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<tr>
<td>Absent</td>
<td>614</td>
<td>1.48 (1.27-1.72)</td>
<td>&lt;0.001</td>
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<tr>
<td>Present</td>
<td>238</td>
<td>1.37 (1.15-1.64)</td>
<td>0.001</td>
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<tr>
<td>Lymph Node Invasion</td>
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<tr>
<td>Negative</td>
<td>805</td>
<td>1.45 (1.28-1.64)</td>
<td>&lt;0.001</td>
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<tr>
<td>Positive</td>
<td>40</td>
<td>1.36 (1.06-1.76)</td>
<td>0.016</td>
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<td>Treatment Modality</td>
<td></td>
<td></td>
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<tr>
<td>Prostatectomy alone</td>
<td>421</td>
<td>1.47 (1.24-1.73)</td>
<td>&lt;0.001</td>
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<tr>
<td>Adjuvant RT</td>
<td>140</td>
<td>1.86 (0.92-3.76)</td>
<td>0.085</td>
</tr>
<tr>
<td>Salvage RT</td>
<td>213</td>
<td>1.44 (1.19-1.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjuvant ADT</td>
<td>44</td>
<td>1.52 (0.97-2.39)</td>
<td>0.068</td>
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<tr>
<td>Salvage ADT</td>
<td>116</td>
<td>1.27 (1.02-1.59)</td>
<td>0.035</td>
</tr>
<tr>
<td>ADT</td>
<td>100</td>
<td>1.33 (1.11-1.61)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

- Hazard ratio per 0.1 (10% increase) in Decipher score
- Decipher improved the ability to predict the cumulative incidence of metastases in nearly all subgroups based on clinicopathologic factors, treatment factors, and demographic factors

Spratt et al., J Clin Onc 2017
Clinical-genomic low risk:
- No difference in 10 yr metastasis between treatment and observation

Clinical-genomic high risk:
- Earlier RT better than late or never.
- Minimal difference in survival between late salvage and observation
Patients with ≥2 risk factors benefit from adjuvant radiation (NNT 3)

-Risk Factors: pT3b/T4, GG4-5, pLN+, Decipher GC>0.6
(Dalela et al JCO 2017)
How Physicians can use Genomics (Decipher) in the Post-Op Setting

Post-Op Prostate Cancer Pathway

Patients with undetectable PSA and 2 or more risk features may be prioritized to adjuvant therapy
- GC>0.6
- pT3b
- pN1
- GS 8-10

NNT with adjuvant to prevent metastasis is 3 (Dalela et al JCO 2017)

- Genomics may also be able to guide intensification of adjuvant therapy (i.e. +/- ADT) and salvage therapies
The Near Future of Genomics in Prostate Cancer
Decipher Platform Provides Genome Wide Data for Bio-Informatics

GRID prospective Decipher Biopsy and RP Patients (n=7,826) : Clustered Drug Response Scores

- Basal active therapy
- Luminal active therapy

- Alkylating (e.g., platinum)
- mTOR (e.g., everolimus)
- Kinase (e.g., cediranib)
- PARP (e.g., olaparib)
- RT-IO (checkpoint)

- Micetubule (e.g., docetaxel)
- Metabolic (e.g., methotrexate)
- HDAC (e.g., belinostat)
- AR (e.g., abiraterone)
Decipher GRID

Hormonal therapy
- ARS
- AR-activity
- NE/SC

Chemo therapy
- Cell proliferation
- DRS
- NE/SC

Immune therapy
- Tcell infiltration
- Checkpoint

Small molecule therapy
- TK inhibitors

Radiation therapy
- PORTOS
- DNA repair

Risk
Patients with high PORTOS have lower rates of metastasis with post-operative radiation

High PORTOS Score (top quartile) = 7 fold better response to radiation after RP

PORTOS is NOT prognostic of metastasis in patients NOT treated by radiation
Androgen Response Signature (Karnes et al in Review)
Cibersort Immune Infiltrates (Zhao et al in Review)
Summary
Genomics – Deciding When and How to Treat Localized Prostate Cancer

- Genomics will greatly improve our treatment of prostate cancer
- Approximately 7% of Gleason Grade Group 1 tumors have molecular features of aggressive disease
  - These men have high GC, GPS or CCP scores
  - Patients with these tumors should approach active surveillance with caution
- Genomics can aid in treatment decisions for men with unfavorable intermediate risk
  - Men with intermediate or high GC scores should prioritize RP +PLND, XRT+sADT or more intense strategies while those with low GC scores (<0.45) may have less intense treatment (i.e. EBRT alone)
- Studies primarily utilizing the Decipher platform are beginning to define radiation sensitivity, androgen sensitivity, immunogenicity and molecular subtypes of prostate cancer
Current Care Strategies Utilizing Genomics

- **NCCN LR or Favorable IR**
- **Considering AS**
- **mpMRI/Fusion Biopsy at 3mo**
- **GG1 or GG2 Genomics**
- **> GG3**
- **Active Surveillance**
- **Treatment**

**Decipher® Biopsy**

- **RP+ePLND**
- **EBRT+ADT**
- **EBRT+ADT + Brachy**
- **Brachy**
- **EBRT**
- **RP+PLND**
- **Subtotal/focal**

**Hi**

**Ave**

**Low**

**Hi**

**Ave**

**Low**

**LP**

**Adverse Path**

- > T3a or + SM

**Discuss Pathology, Order Decipher**

**First PSA @ 2mo**

- Prioritize ART if ≥2 Risk Factors
  - pT3b/T4
  - pLN+
  - GC >0.6
  - GG4-5
Thanks and Questions