Advances in Diagnostic and Molecular Testing in Prostate Cancer

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Disclosures

• Relevant Financial Disclosure
  – Previous Consultant, now Collaborative Researcher: GenomeDX
    • Produces Decipher™ test for post prostatectomy risk assessment
Localized Prostate Cancer – Urologists Perspective

Decision Making Complexity
• High Prevalence
• Broad Spectrum of Localized Disease
• Relatively Long Natural History (Competing Risks)
• Morbidity of Diagnosis and Treatment

Screening and Diagnosis

Surveillance

Treatment

Prostatectomy, Radiation

Surveillance

Adjuvant/Salvage Therapy
PART 1: SCREENING AND DIAGNOSIS
Screening and Diagnosis – Reducing Over Diagnosis

• Strategies—
  – Evidence based screening
    • Decrease intensity of screening (particularly when the screening test is suboptimal)
  – Develop superior tests
    • The ideal test would be able to identify clinically significant prostate cancer
Evidence Based Screening – AUA Statement 2013

• No screening in men under age 40
  – Low prevalence

• Routine screening not recommended for men 40-54
  – Screening can be considered on an individualized basis i.e. men at risk (AAM, +FamHx)

• Shared decision making for screening for men age 55-69
  – Consider routine screening intervals of 2 years or more for men who opt to be screened (PLCO)

• No routine screening in men with <10-15 year life expectancy

• Consider discontinuation of screening at 70
Emerging Approaches for Prostate Cancer Screening / Detection – FDA Approved Tests

- **Prostate Health Index (PHI)**
  - Serum test
  - Approved for use in men 50 and over with PSAs of 4-10 and negative DREs, to help determine if biopsy is indicated

- **PCA3**
  - Urine test
  - Approved for use in decision making for repeat biopsy after a prior negative biopsy (scores <25 protective)
Emerging Approaches for Prostate Cancer Screening/Detection – PHI

- **PHI – Prostate Health Index**
  - Blood test based on total PSA (tPSA), free PSA (fPSA) and the PSA isoform [-2]proPSA
  - \([-2]\text{proPSA} / \text{fPSA} \times \sqrt{\text{PSA}} = \text{PHI}\)
  - proPSA is expressed at greater levels in the peripheral zone (where prostate cancer develops) and also at greater levels from prostate cancer tissue
  - hK2 may be over-expressed in malignancy
  - Increases specificity over a range of sensitivities compared to PSA
  - Cost effective = relatively cheap!

BJU International

September 24, 2015
Emerging Approaches for Prostate Cancer Screening/Detection – PHI


BJU International

September 24, 2015
Above, 350 consecutive RP patients

Similar analysis of ~450 RP patients showed patients with pT3 and GS ≥ 7 have PHI of 64.9 vs 42.9 for those who don’t (p<0.0001) (Fossati et al 2014)
PHI in AAM

- Limited studies
- JHH institutional database
  - 80 AAM who underwent PHI testing and had RP
  - 30 AAM with elevated PSA who underwent PHI testing
Pathologic tumor stage on RP (pT stage):
- pT2
- pT3a (ECE)
- pT3b (SVI)

Pathologic Gleason score:
- Gleason score 6
- Gleason score 7-10
PHI in AAM – Men Undergoing Screening

• 30 AAM presenting with elevated PSA
  – 22 opted not to undergo biopsy
    • Median PHI 19.1 (17-27.5)
  – 8 Underwent prostate biopsy
    • Median PHI 43 (37.5-93.4)
PHI in AAM – Men Undergoing Screening (red = GS 7-10)
Emerging Approaches for Prostate Cancer Screening/Detection – PCA3

- **PCA3**
  - Urine based test for a prostate cancer specific non-coding transcript
  - FDA approved in 2012 for decision making about repeat biopsy in a man with 1 or more negative biopsies
- **Bradley et al J Urol 2013:**
  - A comparative effectiveness review of PCA3 vs PSA commissioned by the US Agency for Healthcare Quality and Research
- **Conclusion:** **PCA3 provides higher accuracy than total PSA and independent information.** Evidence is insufficient that PCA3 testing improves health outcomes
Emerging Approaches for Prostate Cancer Screening/Detection – 4K Score

- Similar to PHI
- Blood test
- Free PSA, Intact PSA, Total PSA, hK2
- AUC increased for any PCa or High Grade vs tPSA (0.79 and 0.82 vs 0.63 and 0.74)
- Prospective screening study is underway
- Most evaluations in European Patients
Emerging Approaches for Prostate Cancer Screening/Detection – Urinary TMPRSS2:ERG

- Chromosomal rearrangement between TMPRSS2 and ETS family members (most notably ERG) seen in ~50% of prostate cancer cases
  - However only ~30% of AAM cases
- Rearrangement produces a unique transcript (tissue based specificity 99.9%)
- Can be analyzed in urine similar to PCA3
- Increases AUC for detection of PCa and High grade disease
Emerging Approaches for Screening/Detection
Multi-Parametric Prostate MRI

T2: anatomy
T2 Images
Diffusion Weighted Imaging
ADC map restricted diffusion

Dynamic Contrast Enhancement
Dynamic Weighted Imaging
Low ADC
Quantitative Parameters from ROI

September 24, 2015
# Multi-Parametric Prostate MRI

<table>
<thead>
<tr>
<th>PI- RADS</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Most Probable Benign</td>
</tr>
<tr>
<td>2</td>
<td>Probable Benign</td>
</tr>
<tr>
<td>3</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>4</td>
<td>Probably Malignant</td>
</tr>
<tr>
<td>5</td>
<td>Highly Suspicious</td>
</tr>
</tbody>
</table>

Portalez et al, E Urol 2012
mpMRI of the Prostate May Play a Significant Role for AAM

- Anterior tumors may be more common among AAM
- mpMRI is imperative for AAM considering AS
- mpMRI may play an important role in prostate cancer screening

Sundi et al. J Urol 2014
Multi-Parametric Prostate MRI

229 men enrolled
3 withdrawals
1: PSA normalized, 2 men refused diagnostic mpMRI

226 men
Diagnostic 3–T mpMRI
T2WI, DWI, ADC, DCE
PI–RADS scoring

83 men
PI–RADS 1 or 2
(No suspicious area on MRI)
2 withdrew; refused TRUSGB

81 men
12–core TRUS–guided prostate biopsy

143 men
PI–RADS 3, 4, or 5
(Suspicious area(s) for cancer on MRI)

143 men
MR–guided biopsy of suspicious lesion(s)
1 man withdrawn: coding

142 men
Blinded 12–core TRUS–guided prostate biopsy immediately after MR–guide biopsy

223 men completed trial
Return to referring urologist for results and management

• Allowed +DRE
• Allowed PSA >10
• 57% PCA on biopsy

• 36% Reduction
Unnecessary Biopsies
• 6% Un-diagnosed
Gleason 7 Dz (3+4=7)

Pokomy et al, E Urol 2014
Clinical Trial of Augmented PSA Screening

PSA 4-10ng/ml, negative DRE

200 men

100 men

Randomization

1:1

100 men

Serum and urine collection, PHI testing

A

TRUS/Bx (std 12 core)

B

mpMRI

A

No Cancer

mpMRI (Follow [B1])

B

PI-RADs ≥ 3

B1

TRUS/MRI Fusion Bx

No Cancer

Very Low / Low-Risk

Int / Hi Risk

B2

PI-RADs < 3

TRUS/Bx (std 12 core)

No Cancer

Very Low / Low-Risk

Int / Hi Risk

No Cancer

Very Low / Low-Risk

Int / Hi Risk
Conclusions Part 1

- PHI, PCA-3, 4K Score, T2:ERG, mpMRI all present opportunities for reduction of over-diagnosis
  - Dedicated studies in AA populations are needed, PHI appears promising
  - mpMRI is imperative for AAM considering AS
- Use in primary unscreened populations is unclear and needs study
- Thresholds for biopsy utilizing new tests needs study
- Comparisons between biomarkers needs study
PART 2: MOLECULAR TISSUE TESTING AFTER DIAGNOSIS
Tissue Based Advances

• Molecular understanding of localized prostate cancer has increased

• We have increased facility to obtain molecular information from routinely collected and stored formalin-fixed paraffin embedded tissue
Molecular Events of Early Prostate Cancer– T2:ERG, Cell Cycle, PTEN Loss

Clonal Evolution

- **NKX3-1** 8p21.2
- **T2-ERG** 21q22.2-3
- **TP53** 17p13.1
- **ETV6** 12p13.2
- **MAP3K7** 6q15
- **CDKN1B** 12p13.1
- **CDKN1A** 6p21.2
- **FOXP1** 3p13

PCAs with deletion

- **NKX3-1**
- **C10orf90**
- **NBPF1**
- **TTN**
- **SPOP**
- **CHD1**

**PTEN** 10q23.31

**time**

Baca et al. Cell 2013
### Table 1. List of 20 Selected Biomarkers Associated With PC Pathogenesis and a Comparison of Their Expression Levels by Ethnicity Using Two Different Statistical Methods

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Function</th>
<th>Mann-Whitney</th>
<th>Logit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERG</td>
<td>Found in 36%-78% of samples; associated with aggressive PC</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>AMACR</td>
<td>Overexpressed in PC relative to benign prostatic tissue</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>SPINK1</td>
<td>Overexpressed in high-grade PC</td>
<td>.001</td>
<td>.028</td>
</tr>
<tr>
<td>NXX3-1</td>
<td>Loss associated with advanced-stage PC and CRPC</td>
<td>.029</td>
<td>.064</td>
</tr>
<tr>
<td>GOLM1</td>
<td>Upregulated in &gt; 90% of PC tissues (unknown function)</td>
<td>.029</td>
<td>.019</td>
</tr>
<tr>
<td>AR</td>
<td>Predictor of decreased biochemical recurrence-free survival</td>
<td>.041</td>
<td>.096</td>
</tr>
<tr>
<td>RB1</td>
<td>Loss coincides with emergence of metastatic CRPC</td>
<td>.077</td>
<td>.097</td>
</tr>
<tr>
<td>GSTP1</td>
<td>Hypermethylated in 60%-80% of PC; in serum, urine, biopsy tissue</td>
<td>.129</td>
<td>.073</td>
</tr>
<tr>
<td>MKi67</td>
<td>Correlates with cancer-specific and overall survival</td>
<td>.129</td>
<td>.115</td>
</tr>
<tr>
<td>FOXP1</td>
<td>Negatively regulates AR signaling in PC</td>
<td>.129</td>
<td>.164</td>
</tr>
<tr>
<td>EZH2</td>
<td>Implicated in the pathogenesis of metastatic PC</td>
<td>.170</td>
<td>.164</td>
</tr>
<tr>
<td>TP53</td>
<td>Exon 6 and 7 mutations correlate with PC tumor progression</td>
<td>.192</td>
<td>.310</td>
</tr>
<tr>
<td>MSMB</td>
<td>Independent predictor of recurrence</td>
<td>.280</td>
<td>.192</td>
</tr>
<tr>
<td>MYCBP</td>
<td>Transcription factor repressor downregulated in PC</td>
<td>.280</td>
<td>.381</td>
</tr>
<tr>
<td>SPOP</td>
<td>Mutations promote AR activity and PC metastatic potential</td>
<td>.280</td>
<td>.381</td>
</tr>
<tr>
<td>FOLH1</td>
<td>Associated with PSA recurrence in high-risk cohort</td>
<td>.347</td>
<td>.326</td>
</tr>
<tr>
<td>TP63</td>
<td>Downregulated in advanced or malignant CRPC</td>
<td>.374</td>
<td>.453</td>
</tr>
<tr>
<td>SRD5A2</td>
<td>A49T, V89L variant correlates with extracapsular disease</td>
<td>.518</td>
<td>.216</td>
</tr>
<tr>
<td>PTEN</td>
<td>Most commonly deleted/mutated tumor suppressor in PC</td>
<td>.855</td>
<td>.724</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Associated with PC occurrence and severity</td>
<td>.855</td>
<td>.964</td>
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</table>

Abbreviations: AR, androgen receptor; CRPC, castration-resistant prostate cancer; Logit, logistic regression; PC, prostate cancer; PSA, prostate-specific antigen.

*P values were adjusted with the Benjamini-Hochberg false discovery rate method.
Genomic Level Pathology of AAM Prostate Cancer May Differ
Differential Prediction of pT3 Disease in AAM and EAM

- **NKK3-1**
  - AA men: $P = 0.025$
  - EA men

- **ERG**
  - AA men: $P = 0.036$
  - EA men

- **AMACR**
  - AA men: $P = 0.036$
  - EA men

- **RB1**
  - AA men: $P = 0.037$
  - EA men

- **FOXP1**
  - AA men: $P = 0.041$
  - EA men

- **GSTP1**
  - AA men: $P = 0.049$
  - EA men
Genomic Level Signatures Maintain Predictive Power
Conclusions Part 2

- Molecular testing of tissue represents an emerging technique to aid in clinical decision making
  - PTEN, OncotypeDX GPS, Promark: AS or Treatment
  - Ki-67, Prolaris: WW vs Treatment
  - Decipher: Adjuvant Radiation

- Molecular basis of prostate cancer may differ by race
- Validation in African American populations is needed and development of ethnicity specific signatures is warranted