IDC-P vs. HGPIN
**ERG**

- *ERG* rearrangement status has been investigated in d.d. between intraductal carcinoma (IDC-P) and cribriform HGPIN

- Cribriform HGPIN consistently lacked *ERG* gene rearrangement while 75% of IDC-P were ERG positive

ERG/PTEN

- Immunostains for PTEN, ERG, p63/CK903 in:
  - 45 IDC-P
  - 15 intraductal cribriform proliferations short of IDC-P
  - 39 HGPIN

- ERG was detected in:
  - 58% of IDC-P
  - 67% of intraductal cribriform proliferations
  - 13% of HGPIN (P<0.0001)

Lotan et al. Mod Pathol 2013;26:587
PTEN loss occurs in ~20-40% of localized PCA but is infrequent in HGPIN.

PTEN loss is found in:
- 84% of IDC-P
- 100% of intraductal cribriform proliferations
- never in HGPIN (P<0.0001)

Cytoplasmic PTEN protein loss has been proposed as a potentially useful marker to distinguish IDC-P from HGPIN.

Lotan et al. Mod Pathol 2013;26:587
Biomarkers useful in predicting risk assessment on prostate needle biopsy

- Best noninvasive tools capable to accurately identify tumors that progress to a more aggressive phenotype
  - Active Surveillance (AS) eligibility
  - Upgrading
  - Disease progression/survival
PTEN loss predicts survival and upgrading

Transatlantic Prostate Group [Cuzick et al. Br J Cancer 2013]
- 675 men on WW; PTEN IHC & FISH (IHC better) on TURP
- 18% PTEN loss in overall cohort
- In low-risk patients, PTEN loss adds prognostic information for prostate survival to GS, PSA, Ki-67 and extent of disease
- Caveat: only 3% of low risk men (GS<7) had PTEN loss

Johns Hopkins Low Grade Cohort [Lotan et al. Mod Path 2015]
- 174 men with GS6 on Bx treated by RP (71 upgraded to GS7; 107 GS6 on RP)
- PTEN IHC on biopsy tissue
- PTEN loss: 18% of upgraded and 7% of not upgraded cases
- OR 3 (1.1-8.6) for upgrading (P=0.035)
**PTEN genomic instability in clinically insignificant and significant PCA**

- PTEN loss analysis for structural variations, point mutations and protein expression in PCA treated by RP:
  - 48 clinically insignificant and 76 significant PCA
- PTEN loss (FISH): 2% of insignificant, 13% of large volume GS6, and 46% of GS≥7
- In GS7 with PTEN loss, alterations were detected in both Gleason pattern 3 and 4
- PTEN loss was associated with ERG fusion and BCR
- PTEN loss was infrequent in insignificant PCA
- PTEN loss in GS6 PCA in needle biopsy indicates a higher likelihood of clinically significant PCA

Murphy SJ et al. Mod Pathol 2016;29(2):143-56
IHC PTEN testing – Outcomes S/P RRP

PTEN+/ ERG neg  0 0 0 0 0 0
PTEN+/ ERG+  1 1 1 1 1 1 1
Any PTEN loss/ ERG neg  — 0 0
Any PTEN loss/ ERG+  0 0 0 0

16% had complete PTEN loss

<table>
<thead>
<tr>
<th>PTEN ERG status</th>
<th>N</th>
<th>Lethal</th>
<th>MVA HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN+ ERG-</td>
<td>442</td>
<td>29</td>
<td>REF</td>
</tr>
<tr>
<td>PTEN+ ERG+</td>
<td>319</td>
<td>15</td>
<td>0.7 (0.4-1.2)</td>
</tr>
<tr>
<td>PTEN- ERG-</td>
<td>79</td>
<td>17</td>
<td>3.8 (2.1-6.9)</td>
</tr>
<tr>
<td>PTEN- ERG+</td>
<td>179</td>
<td>18</td>
<td>1.5 (0.8-2.7)</td>
</tr>
</tbody>
</table>

ERG expression and wild-type PTEN are associated with favorable prognosis and low BCR

- 613 RP specimens
- Median FU 44 months
- BCR in 132 (21.5%) pts.
- ERG+ in 23.7%
- PTEN loss in 41.30%
- BCR-free survival better in ERG+ (P=0.0054); worse with PTEN loss (P=0.1424)
- PTEN loss & ERG+ had worst outcome

Clonal evaluation of PCA foci in biopsies with discontinuous tumor involvement by dual ERG/SPINK1 IHC

- 25% harbored clonally distinct cancer foci
  - 58%: ERG⁺ and ERG⁻ / SPINK1⁻
  - 29%: SPINK1⁺ and ERG⁻ / SPINK1⁻
  - 13%: ERG⁺ and SPINK1⁺
- ERG and SPINK1 overexpression mutually exclusive
- TV in discontinuous core may impact AS eligibility

The Promise of Genomics

Clinical Risk Groups

- Favorable Biology
  - Very Low Risk

- Intermediate

- Unfavorable Biology
  - Intermediate Risk

Add independent predictive information beyond standard clinical and pathologic measures.
**New Biomarkers and Genomic Tests**

- Various tests are available to improve predictive accuracy of PCA detection and risk for clinically significant PCA.
- Each test assesses different but specific set of genes.
- **Challenge** - A biomarker must demonstrate evidence of strong analytical and clinical validity, and clinical utility to enter wide clinical practice (validation!)

<table>
<thead>
<tr>
<th>Who to Biopsy</th>
<th>Who to Rebiopsy</th>
<th>Who to Watch or Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>- PSA</td>
<td>- PCA3</td>
<td>- OncotypeDX</td>
</tr>
<tr>
<td>- PCA3</td>
<td>- Confirm MDx</td>
<td>- Prolaris</td>
</tr>
<tr>
<td>- PHI</td>
<td>- Prostate Core Mitomic Test (PCMT)</td>
<td>- ProMark</td>
</tr>
<tr>
<td>- TMPRSS2-ERG</td>
<td>- 4K score</td>
<td>- Decipher</td>
</tr>
</tbody>
</table>
Confirm MDx for Prostate Cancer (MDxHealth)

- **WHAT is the test?**
  - Detect an epigenetic field effect ("halo") associated with cancerization process at DNA methylation level [GSTP1, APC, RASSF1] in cells adjacent to PCA

- **WHO is the test for?**
  - Patients with negative biopsies

- **WHY do the test?**
  - To decrease unnecessary repeat Bx
  - To identify men at high-risk for occult disease
  - To improve detection of significant PCA following negative biopsy

88-90% NPV

Prolaris Score (Myriad Genetics)

- **WHAT is the test?**
  - Prolaris Score (PS) measures tumor cell growth characteristics providing an assessment of cancer aggressiveness

- **WHO is the test for?**
  - Patients diagnosed with prostate cancer

- **WHY do the test?**
  - To improve risk stratification
  - To identify appropriate patients for AS or immediate treatment (following PBx)
  - To determine postoperative risk of adverse outcome and if treatment is indicated [PS + Capra score improve biochemical recurrence and mortality assessment]

<table>
<thead>
<tr>
<th>Prolaris 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>

Onco
type DX® Prostate Cancer Assay

- **WHAT is the test?**
  - Tumor gene expression assay producing a Genomic Prostate Score (GPS) to help guide initial treatment decisions at time of biopsy

- **WHO is the test for?**
  - Newly diagnosed men with low to low-intermediate risk PCA (GS 3+3, low volume 3+4)

- **WHY do the test?**
  - To improve risk stratification by incorporating tumor biology
  - To identify patients for AS or immediate treatment (high-risk)

Decipher for Prostate Cancer (GenomeDx)

- **WHAT is the test?**
  - Decipher genomic classifier uses a signature of 22 genes (mRNA level)

- **WHO is the test for?**
  - Node-negative high-risk PCA patients managed by RP

- **WHY do the test?**
  - To determine risk of adverse outcome following RP
  - To predicts probability of developing early metastasis (within 5 years) and disease-specific mortality after RP

<table>
<thead>
<tr>
<th>Biological Process</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Cell Adhesion Migration" /></td>
</tr>
<tr>
<td><img src="image" alt="Tumor motility" /></td>
</tr>
<tr>
<td><img src="image" alt="Immune System Modulation" /></td>
</tr>
<tr>
<td><img src="image" alt="Cell Cycle Control" /></td>
</tr>
<tr>
<td><img src="image" alt="Other/Not Known" /></td>
</tr>
</tbody>
</table>

Conclusions

- Molecular and IHC markers play an important role in PCA diagnosis, risk assessment and outcome prediction
- HMWCK/p63 and AMACR are the most commonly utilized IHC markers in clinical practice
- NKX3.1 and GATA3 are useful for diagnosis of poorly differentiated PCA in primary and metastatic setting
- PTEN and ERG may have a possible role in predicting risk assessment on prostate biopsy
- Genomic tests have the potential to improve decision making; further validation of their utility and accuracy is needed with larger multi-institutional studies
Thank you!

magic@ccf.org