Computer-Extracted Features of Gland Morphology from Digital Tissue Images is Comparable to Decipher for Prognosis of Biochemical Recurrence Risk Post-Surgery

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Post-radical prostatectomy treatment

• Adjuvant therapy can extend lives
• Not everyone should get adjuvant therapy
• Precision prescription of adjuvant therapy could reduce deaths and overtreatment
Standard-of-care: Nomograms

• Require a pathologist
• Vulnerable to intra- and inter-reviewer variability
• Do not provide perfect stratification
Companion diagnostics

- Molecular tests of tissue
- Tissue-destructive, no retesting
- Expensive ($4000)
- Not widely available

Table 1. Available Tissue-Based Tests for Prostate Cancer Risk Stratification/Prognosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Platform</th>
<th>Populations Studied</th>
<th>Outcome(s) Reported (Test independently predicts)</th>
<th>Selected References</th>
<th>Molecular Diagnostic Services Program (MolDX) Recommendations</th>
</tr>
</thead>
</table>
| Decipher  | Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue | Post RP, adverse pathology/ high-risk features, Post RP, biochemical recurrence, Post RP, adjuvant, or salvage radiation, Biopsy, localized prostate cancer post RP or EBRT | • Metastasis  
• Prostate cancer-specific mortality  
• PORTOS  
• Metastasis  
• Prostate cancer-specific mortality  
• PORTOS  
• Metastasis  
• Prostate cancer-specific mortality  
• Gleason grade ≥4 disease at RP  
• Adverse pathologic features at RP | 136,139,140,234–249 | Cover postbiopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment of prostate cancer and are candidates for active surveillance or definitive therapy  
Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir) |
Quantitative histomorphometry

• Digitized H&E specimens
• Sub-visual features
• Useful for
  • Prostate BCR prognosis, grading
  • Prostate, breast, lung cancer detection
Histotyping: A computerized visual assay

• Hypothesis: Quantitative features of lumen morphology are prognostic of BCR
• Computer analysis of digitized slides
• Use both features known to pathologists and those not currently examined
• Compare Histotyping to Decipher companion diagnostic test
Dataset

• Radical prostatectomy specimens
• Inclusion criteria: post-surgery PSA testing, no adjuvant therapy
• One slide per patient annotated for tumor region
• N=381 patients split into:
  • n=214 training set from University of Pennsylvania, University Hospitals
  • n=167 validation set from University of Pennsylvania, Mount Sinai
Histotyping model construction

Feature extraction

Stability filtering

Patient X

Risk score

Feature 1
Feature 2
Feature 3
Feature 4

Cox regression

Histotyping score

Include Gleason grade and PSA for Histotyping+
Features used in Histotyping

- 5 features of lumen shape, 1 feature of lumen arrangement
- Prevalence of disk-shaped lumen associated with worse outcomes

Low lumen circularity
High lumen circularity
Results: Histotyping vs. Decipher

Histotyping (c-index = 0.68)

- Low-risk: 79 (0) 19 (52) 0 (69)
- High-risk: 88 (0) 19 (43) 2 (55)

Decipher (c-index = 0.70)

- Low-risk: 71 (0) 19 (42) 1 (54)
- Inter.-risk: 37 (0) 13 (21) 1 (32)
- High-risk: 59 (0) 6 (32) 0 (38)

HR L/I = 0.45 (0.21 - 0.96)
HR I/H = 4.86 (2.10 - 11.24)

p = 0.0047
HR = 2.60 (1.41 - 4.81)
Results: Histotyping vs. Decipher

Histotyping (c-index = 0.68)

Decipher (c-index = 0.70)

Number at risk (number censored)

<table>
<thead>
<tr>
<th></th>
<th>Low-risk</th>
<th>High-risk</th>
<th>Low/inter.-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>79 (0)</td>
<td>88 (0)</td>
<td>108 (0)</td>
<td>59 (0)</td>
</tr>
<tr>
<td>Censored</td>
<td>19 (52)</td>
<td>19 (43)</td>
<td>0 (69)</td>
<td>2 (86)</td>
</tr>
<tr>
<td></td>
<td>19 (55)</td>
<td>2 (55)</td>
<td></td>
<td>6 (32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 (38)</td>
</tr>
</tbody>
</table>

p = 0.0047
HR = 2.60 (1.41 - 4.81)

p = 0.00055
HR = 2.73 (1.38 - 5.41)
Results: Histotyping+ vs. Decipher

Histotyping+ (c-index = 0.75)

- **Low-risk**: 83 (0)  
  - Number at risk (number censored): 21 (57)  
  - Number at risk (number censored): 0 (74)

- **High-risk**: 84 (0)  
  - Number at risk (number censored): 17 (38)  
  - Number at risk (number censored): 2 (50)

HR = 3.77 (2.04 - 6.96)

Decipher (c-index = 0.70)

- **Low-inter.-risk**: 108 (0)  
  - Number at risk (number censored): 32 (63)  
  - Number at risk (number censored): 2 (86)

- **High-risk**: 59 (0)  
  - Number at risk (number censored): 6 (32)  
  - Number at risk (number censored): 0 (38)

HR = 2.73 (1.38 - 5.41)
Conclusions

- Histotyping was prognostic of BCR
- Performance similar to Decipher
- Computer analysis of morphology could supplement existing prognostic tools
- Future work: Predictive of treatment response, metastasis outcome
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