Identifying Gene Expression to Predict Biochemical Recurrence Following Radical Prostatectomy

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Disclosures

- JRW
  - Medtronic: Consulting
  - Genomic Health: Speaker
  - Decipher Biosciences: Speaker
For patients undergoing radical prostatectomy, ~1/3 will eventually require additional treatment\(^1\)

Patients with higher risk prostate cancer may initially be undertreated\(^2\) and miss the treatment window before developing metastatic disease

The urologic community needs a way to distinguish which patients deserve the most aggressive treatment upfront

Biomarkers such as Decipher may help determine which patients may benefit from further treatment

To date, there has been no consensus for a superior predictive model to predict prostate cancer recurrence


Between 2008 and 2011, patients undergoing radical prostatectomy at Hartford Hospital were consented to submit specimens for whole genome gene expression as part of the Total Cancer Care Consortium.

RNA isolated from formalin-fixed paraffin-embedded prostates was hybridized to a custom Affymetrix microarray.

Regularized (LASSO) Cox regression was performed with cross-validation to identify a gene expression signature that improves risk prediction.

Recurrence was defined as post-operative PSA >0.2 ng/mL or triggered salvage treatment.

Model performance was assessed using time-dependent ROC curves and survival plots.
<table>
<thead>
<tr>
<th></th>
<th>No BCR (N = 501)</th>
<th>BCR (N = 105)</th>
<th>p-value</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.8 ± 6.2</td>
<td>61.1 ± 5.8</td>
<td>0.04168</td>
<td>t-test</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td>0.6528</td>
<td>Fisher exact</td>
</tr>
<tr>
<td>White</td>
<td>408 (81.4%)</td>
<td>92 (87.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>12 (2.4%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>13 (2.6%)</td>
<td>3 (2.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>68 (13.6%)</td>
<td>10 (9.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic PSA</td>
<td>4.9 (4.1, 6.6)</td>
<td>5.7 (4.2, 7.4)</td>
<td>0.02313</td>
<td>t-test on log</td>
</tr>
<tr>
<td>Specimen (grams)</td>
<td>51 ± 16.6</td>
<td>48.7 ± 14.2</td>
<td>0.1849</td>
<td>Mann-Whitney U</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td>1.752E-11</td>
<td>Fisher exact</td>
</tr>
<tr>
<td>pT2a</td>
<td>38 (7.6%)</td>
<td>1 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2b</td>
<td>12 (2.4%)</td>
<td>1 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2c</td>
<td>342 (68.3%)</td>
<td>43 (41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT3a</td>
<td>92 (18.4%)</td>
<td>44 (41.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT3b</td>
<td>16 (3.2%)</td>
<td>16 (15.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT4</td>
<td>1 (0.2%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason sum</td>
<td></td>
<td></td>
<td>2.973E-14</td>
<td>Fisher exact</td>
</tr>
<tr>
<td>6</td>
<td>153 (30.5%)</td>
<td>9 (8.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>327 (65.3%)</td>
<td>66 (62.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>10 (2%)</td>
<td>13 (12.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>11 (2.2%)</td>
<td>17 (16.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive margins</td>
<td>100 (20%)</td>
<td>30 (28.6%)</td>
<td>0.06818</td>
<td>Chi-squared</td>
</tr>
<tr>
<td>D'Amico Risk</td>
<td></td>
<td></td>
<td>6.132E-11</td>
<td>Chi-squared</td>
</tr>
<tr>
<td>Low</td>
<td>228 (45.5%)</td>
<td>21 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>220 (43.9%)</td>
<td>48 (45.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>53 (10.6%)</td>
<td>36 (34.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Modeling Approach

• Use regularized LASSO (least absolute shrinkage and selection operator) Cox regression to identify a gene expression signature that improves risk prediction

  – Start with all genes in the model, use a penalty to shrink coefficients

  – Will shrink coefficients to zero, performing variable selection

  – Provides adjusted coefficients to reduce overfitting
Performance of Unique Genomic Signature

AUC (Path + Signature) v (Path)

AUC = 0.868
AUC = 0.767

PSA Recurrence Low v. High Risk Signature

HR = 9.6 (95% CI 6 to 15.4)
p < 2e-16

Risk score = 0.5(Gleason) + 0.32(Stage) - 0.2(CNRIP1) - 0.22(ERP44) + 0.29(MTX2) + 0.23(RHOU) + 0.21(OXR1)
Genes in LASSO model

- **RHOU**\(^3\): Ras homolog family member U
  - Found **increased** in PCa, silencing in PCa cell lines resulted in growth arrest and cytotoxicity
  - Downstream of JAK/STAT signaling; mediates cell migration in multiple myeloma
- **MTX2**\(^4\): Metaxin-2
  - Mitochondrial transport; protein found **increased** in PCa
- **ERP44**\(^5\): Endoplasmic reticulum protein 44
  - Protein expressed at **higher** level in PCa (vs BPH)
  - Chaperone in secretory pathway; inhibits lung cancer cell migration
- **CNRIP1**\(^6\): Cannabinoid receptor interacting protein 1
  - Non-habit-forming cannabinoid receptor agonists have been suggested for prostate cancer treatment
  - Promoter hyper-methylated in colorectal cancer, correlated with aggressiveness
- **OXR1**\(^7\): Oxidation resistance 1
  - Prevents oxidative stress-induced cell death

Risk score = 0.5(Gleason) + 0.32(Stage) - 0.2(CNRIP1) - 0.22(ERP44) + 0.29(MTX2) + 0.23(RHOU) + 0.21(OXR1)

3-7: References available on request
Model Validation

MSKCC data set

32 samples with recurrence
104 samples no recurrence

BCR defined as PSA ≥ 0.2 ng/ml on two occasions

Includes Gleason, pathology stage, PSA progression (with time to recurrence or censor)

*Different microarray
LASSO model: Model validation set GSE21034 MSKCC

HR = 9.3 (95% CI 3.6 to 24.3)
\( p = 2.7 \times 10^{-8} \)

\[ \text{AUC} = 0.839 \]
Model Validation

ICR data set

23 samples with recurrence
57 samples no recurrence

BCR defined as PSA ≥ 0.2 ng/ml or triggered salvage

Includes Gleason, pathology stage, PSA progression (with time to recurrence or censor)

*Different microarray
LASSO model: Model validation set GSE94767 ICR

HR = 4.8 (95% CI 1.8 to 13.2)

p = 7.4e-4
Discussion

- PSA threshold for recurrence: MSKCC used classic value of 0.2. We (and ICR) used 0.2 or salvage treatment (75% of our patients currently receive salvage radiation with a PSA less than 0.2)

- Median follow up time was 60 months

- Sample population underwent radical prostatectomy between 2008 and 2011; many patients today would choose AS over RALP
Conclusion

- Using a large sample of radical prostatectomy specimens, a gene expression signature was identified that predicts BCR.

- The prediction model was validated on two independent gene expression data sets and surpassed Gleason grade and tumor stage alone.

- The prediction model has a similar AUC to commercially available tests that incorporate pathologic parameters and gene signatures; further studies are required to compare the results of our study against other predictive models and other genomic tests.

- The five gene signature includes three genes that have previously been identified as associated with high risk prostate cancer as well as two additional genes that to our knowledge have not been previously identified.

- Potential for gene targeted therapy.
Thank You