Identification and Validation of Intrinsic Subtypes of Prostate Cancer

D. E. Spratt¹, S. G. Zhao¹, S. L. Chang¹, M. R. Cooperberg², N. G. Erho³, C. Speers⁴, R. Mera¹, Y. S. Niknafs¹, P. L. Nguyen⁵, R. B. Den⁶, A. P. Dicker⁶, E. A. Klein⁷, R. J. Karnes⁸, E. M. Schaeffer⁹, E. Davicioni³, P. Carroll², A. Chinnaiyan¹⁰, S. A. Tomlins¹, A. E. Ross⁹, F. Y. Feng¹¹

¹University of Michigan, Ann Arbor, MI, ²University of California, San Francisco, San Francisco, CA, ³GenomeDx Biosciences, Vancouver, BC, Canada, ⁴Veteran Affairs Hospital Ann Arbor, Ann Arbor, MI, ⁵Brigham & Women’s Hospital, Dana Farber Cancer Institute and Harvard Medical School, Boston, MA, ⁶Sidney Kimmel Medical College at Thomas Jefferson University, Sidney Kimmel Cancer Center, Philadelphia, PA, ⁷Cleveland Clinic, Cleveland, OH, ⁸Mayo Clinic, Rochester, MN, ⁹Johns Hopkins University, Baltimore, MD, ¹⁰The University of Michigan Cancer Center, Ann Arbor, MI, ¹¹University of California at San Francisco, San Francisco, CA
Background

• Currently, risk grouping systems for prostate rely on imperfect tools, such as the digital rectal exam, to group patients by risk of recurrence.

• These systems do not provide information of the biology of the disease, do not always provide accurate prognostic information, and cannot assess which patient will truly benefit from our therapies.

• The goals of our project were to:
  1. Identify the intrinsic molecular subtypes of primary prostate cancer through tumor sequencing with an unbiased approach.
  2. Determine the prognostic significance of the molecular subtypes.
  3. Understand if the subtypes could predict who would benefit from post-operative radiotherapy.
Method

Cohorts 1-7

- Source: Mayo I and II, Cleveland Clinic, Johns Hopkins, Thomas Jefferson, Erasmus, and MSKCC
- Design: Retrospective
- N=1626
- Platform: Affymetrix microarray
- Storage: FFPE and Fresh Frozen

Cohort 8

- Source: The Cancer Genome Atlas (TCGA)
- Design: Prospective
- N=497
- Platform: RNAseq
- Storage: Fresh Frozen

Cohort 9

- Source: Decipher GRID™
- Design: Prospective
- N=2113
- Platform: Affymetrix microarray
- Storage: FFPE

Total Samples: 4236
The results show that 100 genes were identified in the prospective validation.

The 3 intrinsic molecular subtypes were identified.
Results

Subtype A has the lowest rate of Distant Metastases

Additional variables in MVA: Age, PSA, Gleason, surgical margins, ECE, SVI, and LNI

Multivariable Analysis

<table>
<thead>
<tr>
<th>Co-variables</th>
<th>HR [95% CI]</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Subtype B vs. A</td>
<td>1.31 [1.03-1.65]</td>
<td>0.03</td>
</tr>
<tr>
<td>Subtype C vs. A</td>
<td>1.33 [1.04-1.71]</td>
<td>0.02</td>
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</tbody>
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Multivariate Interaction with RT

<table>
<thead>
<tr>
<th>Variable Interaction of RT: Group A vs. B+C</th>
<th>Hazard Ratio</th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>0.44</td>
<td>0.002</td>
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Subtypes B+C have a significantly improved response to post-operative RT than subtype A.
Conclusions

• We have identified the 3 intrinsic molecular subtypes of primary prostate cancer and rigorously validated them to show that they are highly reproducible.

• These subtypes can independently predict the risk of a patient developing distant metastasis after a radical prostatectomy.

• These subtypes appear to be able to predict who will respond most favorably to post-operative radiotherapy.

• The molecular subtypes will help us to personalize care for each prostate cancer patient to help inform us of their risk of recurrence and their potential benefit from radiation therapy.