Impact of distinct tumor lineage models on prostate cancer prognosis

**Deli Liu**, Michael A. Augello, Jonathan E. Shoag, Davide Prandi, Yang Liu, Francesca Demichelis, Elai Davicioni, Andrea Sboner, Christopher E. Barbieri

1 Department of Urology, Weill Cornell Medicine, New York, NY, USA
2 Sandra and Edward Meyer Cancer Center, Weill Cornell Medicine, New York, NY, USA
3 Centre for Integrative Biology, University of Trento, Via Sommarive 9, 38123, Trento Italy.
4 GenomeDx Bioscience Inc., Vancouver, British Columbia, Canada.
5 Engleman Institute for Precision Medicine of Weill Cornell Medicine and NewYork-Presbyterian Hospital, New York, NY, USA.

**Background**
Molecular characterization of prostate cancer (PCa) has revealed several subclasses based on underlying genomic alterations. Understanding the role of these molecular subclasses on prostate cancer progression remains elusive.

**Methods**
Here we hypothesized that two distinct tumor lineage models of PCa progression involved ERG/PTEN and SPOP/CHD1, with PTEN and CHD1 deletions as markers of subtype-specific progression events, respectively. To test our hypothesis, we developed two SCaPT (SubClass Predictor Based on Transcriptional Data) models to classify progression events of PTEN and CHD1 deletions purely from transcription data with high confidence. We then classified molecular subclasses from retrospective and prospective cohorts of 8,158 patients via SCaPT models and decision tree.

**Results**
We found transcriptional alterations pointed to both shared and lineage specific signaling pathways between two tumor lineage models. After classifying molecular subclasses from Decipher cohort, we found progression events of PTEN and CHD1 deletions showed worse prognostic outcomes, when compared to early events of ERG fusion and SPOP mutation, consistent with our model of lineage-specific tumor progression. Strikingly, the association between PTEN deletion and adverse pathologic features at radical prostatectomy, e.g. higher Gleason score, extracapsular extension, seminal vesicle invasion, lymph node invasion, and T3 or T4 cancer stages, was significantly different in the case of CHD1 deletion, where only high Gleason score was associated to this molecular event.

**Conclusions**
These findings suggest a paradigm in which specific subtypes of prostate cancer follow distinct lineage models of progression, at both the molecular and clinical levels. Therefore, the interpretation of common risk stratification parameters such as TNM staging may be influenced by the underlying distinct tumor lineages models and molecular subclasses of prostate cancer.

**Conflict of Interest**

Yang Liu  
Employment: GenomeDx  
Elai Davicioni  
Employment: GenomeDx; Leadership: GenomeDx; Stock and Other Ownership Interests: GenomeDx; Patents, Royalties, Other Intellectual Property: Cancer diagnostics using biomarkers 20140066323; Travel, Accommodations, Expenses: GenomeDx.

Christopher E. Barbieri  
Patents, Royalties, Other Intellectual Property: Coinventor on a patent application filed regarding SPOP mutations in prostate cancer by Weill Cornell Medicine.

**Funding Acknowledgements**

This work was supported by: the Prostate Cancer Foundation (C.E.B), NCI (P50CA211024-02, C.E.B.), a Urology Care Foundation Rising Star in Urology Research Award (C.E.B.), Damon Runyon Cancer Research Foundation MetLife Foundation Family Clinical Investigator Award (C.E.B.), and the Prostate Cancer Foundation Young Investigator Award (D.L.).