

Validation of gene expression signatures for genomic identification of neuroendocrine prostate cancer

Samar A. Hegazy¹, Alexander W. Wyatt², Jonathan Lehrer³, Hatem Abo Ouf¹, Mohammed Alshalafa³, Ewan A. Gibb³, Beatrix Palmer-Arontsen³, Nicholas Erho³, Elai Davicioni³, Harrison Tsai⁴, Tamara L. Lotan⁴ and **Tarek A. Bismar**¹

¹Department of Pathology and Laboratory Medicine, University of Calgary and Calgary Laboratory Services, Calgary, Alberta, Canada

²Vancouver Prostate Centre and Department of Urologic Sciences, University of British Columbia, Canada

³GenomeDx Biosciences Inc., Vancouver, Canada

⁴Pathology and Oncology, Johns Hopkins School of Medicine, Baltimore, MD, United States

Background: Neuroendocrine prostate cancer (NEPC) is a rare, aggressive variant of PC with rapid progressive clinical course and resistance to androgen deprivation therapy (ADT). Early identification of patients harboring tumors with NEPC-like genomic profiles is of significant interest and could be useful in guiding optimal therapy.

Methods: The Decipher GRID was queried for two signatures that have been previously reported to predict NE-status (Kumar et al. and Alshalafa et al., 2016) as well as expression levels of four genes known to be associated with NE disease (RB1, CCND1, CHGA, AURKA). The signatures were evaluated in a retrospective cohort of 16 men diagnosed with *de novo* NEPC and RP specimens from a prospective cohort of 2,829 men with localized adenocarcinoma. Both cohorts were profiled with the Decipher assay (GenomeDx Biosciences Laboratory, San Diego, CA). The molecular signatures and genes associated with NE disease were compared between the two cohorts using the area under the receiver operating curve (AUC) metric.

Results: Consistent with known NEPC gene expression patterns, expression of RB was lower and expressions of CHGA and AURKA were higher in the neuroendocrine as compared to the adenocarcinoma cohort (AUC=0.77, 0.80, 0.80 respectively, $p < 0.001$). Expression of CCND1 trended lower in the neuroendocrine cohort (as expected), but failed to attain significance (AUC=0.64, $p=0.056$). NEPC signature scores were consistently higher in the neuroendocrine compared to the adenocarcinoma cohort with AUCs of 0.91 and 0.92 for the Alshalafa and Kumar signatures, respectively ($p < 0.001$). Based on previously reported cut-offs, 3.6% and 2.1% of patients had outlier NEPC scores for Alshalafa and Kumar signatures, respectively in the prospective cohort.

Conclusions: The previously reported NEPC signatures demonstrated promise as tools to discriminate between PCa and NEPC. With validation in additional larger cohorts and implementation in a clinical-grade genomic assay, these signatures may aid clinicians with improved identification of NEPC. Future studies will assess molecular differences in primary tumors at highest risk for NEPC differentiation post XRT/ADT therapy. Molecular signatures are warranted to aid in stratifying patients for therapeutic options.

Conflict of Interest: JL, MA, EG, NE, ED are employees of GenomeDx Biosciences.

Funding Acknowledgements: PCF young Investigator award (TAB)