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Prostate cancer gene expression panel to address racial differences of molecular alterations in prostate cancer

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Introduction and Objectives: Prostate cancer (CaP) affects 1 in 7 men in their life time. African American (AA) men have significantly higher incidence and mortality from CaP compared to Caucasian American (CA) men. Emerging data including ours have described significantly lower frequencies of alterations in common CaP driver genes (*ERG* and *PTEN*) in AA men as compared to CA men. We have also noted that genes commonly overexpressed in CaP (*ERG*, *AMACR*, *PCA3*), and currently used as diagnostic markers, exhibit much lower frequency and more heterogeneity in AA men. The goal of this study was to define a CaP marker panel that is overexpressed equally well in AA and CA CaP.

Methods: Three platforms (RNASeq, NanoString and qRT-PCR) were used for evaluation of CaP associated gene expression in CA and AA patients (N=144). Candidate genes with robust tumor overexpression (over 4-fold) in CaP in paired normal and tumor specimens from AA and CA patients were selected from Nanostring and RNASeq data for validation by qRT-PCR (TaqMan) in laser microdissected (LCM) tumor and benign cells of frozen tissue sections (50 CA and 35 AA). An assay protocol (gene specific RT and pre-amplification followed by TaqMan PCR) was set up for noninvasive early detection of candidate genes in regular patient urine (non-DRE) using urinary exosomal RNA.

Results: As expected tumor transcriptomes of CA patients consistently revealed elevated expression of *PCA3* and *AMACR*. However, these genes had variable overexpression in AA cohort. The top genes that were similarly over expressed in tumors of AA and CA patients were validated by qRT-PCR in LCM tumor and normal epithelial cells (N=85). At least one gene of a six-gene signature (*DLX1, HOXC4, NKX2-3, COL10A1, HOXC6* and *PSGR*) was overexpressed in tumor cells of all AA and CA cases, providing a consistent ethnicity informed tumor expression signature, which was further validated in silico in TCGA RNASeq data. Urinary exosome based assay was developed and optimized for *PSGR, DLX1, HOXC4, NKX2-3, as well as PCA3*, *PCGEM1* and *ERG*. All markers have been evaluated in a prospective cohort of 100 patients. In 36 AA patients a sensitivity of 78%, specificity of 68%, and AUC of 0.83 was achieved surpassing currently used urine CaP markers of *ERG* and *PCA3*.

Conclusions: A CaP tissue based gene expression marker panel has been defined with potential diagnostic utility for both CA and AA men in the context of urinary exosomes

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