Interim performance of a non-DRE urine exosome gene signature to predict Gleason ≥7 prostate cancer on initial prostate needle biopsy from patients enrolled in a prospective observational trial.

Abstract #5064
Board #58

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Introduction:

Prostate cancer (PCa) is the second leading cause of cancer death among men in the United States, with an anticipated 233,000 new cases and nearly 29,480 deaths in 2014. The definitive diagnostic for PCa is the prostate needle biopsy, typically recommended for men with elevated serum prostate-specific antigen (PSA levels) and/or a suspicious digital rectal exam (DRE) with added indication from family history, age, and race. The majority of prostate cancers remain indolent, infrequently resulting in death; thus, there is a major risk for detecting cancers that are clinically insignificant and don't require treatment. Unfortunately, due to the low positive predictive value (PPV) of PSA and the high prevalence of low risk PCa, approximately 70% to 80% of men will undergo an unnecessary biopsy. Non-invasive screening tools that add predictive value for identifying high-grade, Gleason score (GS) ≥7 should impact on the current diagnostic paradigm. Here, we sought to evaluate the performance of a gene signature that differentiated GS7+ from GS6 + benign disease by evaluating patients with first-time biopsy results and gray zone PSA (4-10ng/mL) from an ongoing prospective clinical trial.

Methods:

The study population consisted of men aged ≥40 years scheduled for an initial or repeat prostate needle biopsy, due to a suspicious DRE and/or PSA levels, and met the eligibility criteria. For this analysis we focused on men who were undergoing their initial biopsy and had an equivocal 'gray zone' serum PSA levels (>4 and <10 ng/ml). 499 sequentially obtained first-catch non-DRE urine specimens were collected at 15 sites in standard collection vessels without preservative, stored at 2-8C (for up to two weeks), and shipped on ice to a central laboratory. Upon receipt, samples were filtered (0.8um), and exosome isolation and RNA extraction performed. RT-qPCR RNA copy numbers of ERG and PCA3, normalized to SPDEF, were measured to generate a three-gene signature, defined to yield an EXO106 score between 0 and 30, where >10 predicts >GS7 vs. GS6 and benign lesions with optimal NPV, Sensitivity, and Specificity (Figure 1).

Results:

Urine samples from 205 of the 499 patients enrolled had a urine volume <50ml, PSA between 4-10 ng/mL, and were presenting for their initial biopsy. The cohort had the following demographics: median age 64 years, median PSA 5.46 ng/mL, 80% negative DRE, 74% no family history, 68% Caucasian. There was a 50% positive biopsy rate (all cancer) with a 33% >GS7 disease. A dichotomous EXO106 score (i.e. gene signature + standard of care = PSA, Age, Ethnicity, Family History) demonstrated good clinical performance in predicting the biopsy result.

For >GS7, with a 90% fixed sensitivity, the NPV and PPV were 92% and 48%, respectively, compared to 79% and 35% for the prostate cancer prevention trial risk calculator (PCPTRC) (Table 1). A continuous EXO106 score alone had an AUC of 0.74 for discriminating >GS7 from GS6 and benign disease and the results were significantly better than the performance of the PCPTRC, AUC 0.64 (p = 0.026; Figure 3).

TABLE 1: Comparison of EXO106 combined with SOC to the PCPTRC

Binary Performance Parameters of EXO106+SOCand PCPTRC in predicting High Grade Cancer (GS≥7, N=205)

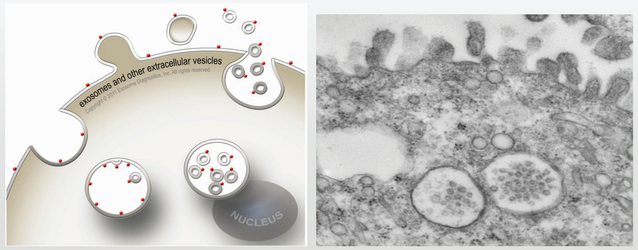
	Sensitivity% (Locked at 90)	Specificity% (95% CI)	NPV% (95% CI)	PPV% (95% CI)
EXO106 + SOC*	90	51.8 (43.5-60.2)	92.2 (86.2-98.2)	48.4 (39.8-57.1)
Prostate Cancer Prevential Trial -Risk Calculator (PCPTRC)	90	16.8 (10.5-23.0)	79.3 (64.6-94.1)	35.2 (28.2-42.1)

NPV=negative predictive value, PPV=positive predictive value

*The score EXO106 + SOC is derived from a joint logistic regression model of EXO106 with the following standard of care parameters (numerical encoding in brackets): Age (years), Ethnicity (African-America yes=1, no=0), family history (yes=1, no=0), and Serum PSA ($\log_2$ PSA level). Logistic regression model was derived on a earlier data set.

FIGURE 1: Exosomes: Rich Source of Molecular Details

- **Exosomes and microvesicles are secreted by virtually all cells into all biofluids, as an active process of cellular communication.**
- **Exosomes are lipid bilayer protected vesicles, which makes them stable under varying conditions and protects their contents from degradation.**
- **Exosomes contain RNA (mRNA, microRNA, tRNA, rRNA, lncRNA, and other RNA species), DNA, and protein.**



Miranda K et al., Kidney International 2010; 78:191-199.

FIGURE 2: EXO106 Urine-Based Liquid Biopsy Test

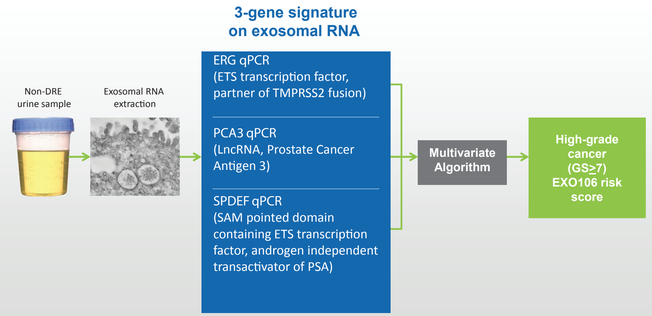
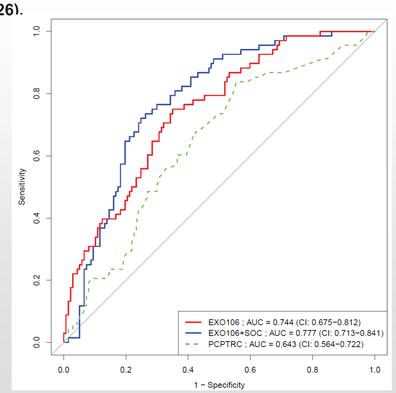


FIGURE 3: A continuous EXO106 Score (with and without SOC) is predictive for discriminating GS6 and benign disease from >GS7 cancer (AUC 0.77 and 0.74, respectively), and these results were significantly better than the PCPTRC on the same patient group (AUC 0.64, p=0.026).



Conclusions:

We confirmed a novel, non-invasive urine exosome gene signature demonstrated independent, negative predictive value for the diagnosis of GS7+ from first biopsy patients with 'gray zone' PSA. Its use in the biopsy decision process should result in fewer prostate biopsies pending completion of the prospective trial. A large clinical validation study of EXO106 that enrolled more than 1,000 patients has been completed and the data presented.

References:

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