Clinical Use of PCA3 and TMPRSS2:ERG Urinary Biomarkers in African-American Men Undergoing Prostate Biopsy

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Purpose: Prostate specific antigen has decreased performance characteristics for the detection of prostate cancer in African-American men. We evaluated urinary PCA3 and TMPRSS2:ERG in a racially diverse group of men.

Materials and Methods: After institutional review board approval, post-examination urine was prospectively collected before prostate biopsy. PCA3 and TMPRSS2:ERG RNA copies were quantified using transcription mediated amplification assays (Hologic, San Diego, California). Prediction models were created using standard of care variables (age, race, family history, prior biopsy, abnormal digital rectal examination) plus prostate specific antigen. Decision curve analysis was performed to compare the net benefit of PCA3 and TMPRSS2:ERG.

Results: Of 304 patients 182 (60%) were African-American and 139 (46%) were diagnosed with prostate cancer (69% African-American). PCA3 and TMPRSS2:ERG scores were greater in men with prostate cancer, 3 or more cores, 33.3% or more cores, greater than 50% involvement of greatest biopsy core and Epstein significant prostate cancer ($p < 0.01$). PCA3 added to the standard of care plus prostate specific antigen model for the detection of any prostate cancer in the overall cohort (0.747 vs 0.677, $p < 0.0001$) in African-American men only (0.711 vs 0.638, $p=0.0002$) and nonAfrican-American men (0.781 vs 0.732, $p=0.0016$). PCA3 added to the model for the prediction of high grade prostate cancer for the overall cohort (0.804 vs 0.78, $p=0.0002$) and African-American men only (0.759 vs 0.717, $p=0.0003$) but not nonAfrican-American men. Decision curve analysis demonstrated improvement with the addition of PCA3.

Abbreviations and Acronyms

AA = African-American
CA = Caucasian American
DCA = decision curve analysis
DRE = digital rectal examination
PCa = prostate cancer
PSA = prostate specific antigen
PSAD = PSA density
SOC = standard of care
T2:ERG = TMPRSS2:ERG gene fusion

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For African-American men TMPRSS2:ERG did not improve concordance statistics for the detection of prostate cancer.

Conclusions: For African-American men urinary PCA3 improves the ability to predict the presence of any and high grade prostate cancer. However, the TMPRSS2:ERG urinary assay does not add significantly to standard tools.

Key Words: biomarkers; prostate cancer antigen 3, human; prostatic neoplasms; African Americans; biopsy

PROSTATE cancer is the most commonly diagnosed malignancy and the second leading cause of cancer related death for American men. For African-American men PCa is more prevalent and more deadly. AA men have an age adjusted incidence of PCa twice that of Caucasian American men (214.5 vs 130.4 per 100,000 males in 2012), and an age adjusted annual PCa death rate 2 to 3 times that of CA men (46.3 vs 19.8 per 100,000 males in 2012).[1] This represents the largest racial disparity of any malignancy. While some of these disparate findings are due in part to issues with socioeconomic status, inherent differences remain in the incidence and mortality of prostate cancer between AA and CA men.[2]

More than 1 million biopsies are performed yearly in the United States, largely based on increased PSA, with fewer than 25% resulting in a positive finding.[3] PSA testing lacks sensitivity and specificity, leads to the over detection and overtreatment of low risk cancers, and increases exposure to the harms of a biopsy.[4] Additionally, PSA has been shown to have decreased accuracy in AA men.[5–7] In 2012 the U.S. Preventive Services Task Force recommended against PSA screening for all men in the United States regardless of race. This recommendation was largely based on the results of 2 trials, of which only 4% of participants were AA.[8–10]

The PCA3 test is a urine assay that detects the over expression of Prostate Cancer Gene 3, prostate specific noncoding mRNA that is over expressed in patients with PCa. The test is commercially available in the United States for men with a negative biopsy but still at risk for PCa. The TMPRSS2:ERG gene fusion is a PCa specific DNA rearrangement in which 5′ untranslated transmembrane protease serine 2 (TMPRSS2), an androgen regulated gene, fuses with ERG, a member of the ETS transcription family, resulting in the up-regulation of ERG. Like PCA3, T2:ERG mRNA can be detected in urine.

Urinary assays for PCA3 and T2:ERG are established biomarkers for the detection of PCa. PCA3 and T2:ERG have been shown to increase the accuracy of the prediction of biopsy outcomes in men with increased serum PSA. However, the evidence of their usefulness relies almost entirely on studies of men of European ancestry. We sought to prospectively determine the performance characteristics of PCA3 and T2:ERG in a racially diverse group of men undergoing prostate biopsy.

METHODS

From December 2013 to June 2015 post-DRE urine was prospectively collected from patients at 3 inner-city New Orleans hospitals before 12 to 14-core prostate biopsy. Biopsies were performed for abnormal DRE or increased PSA. All consecutive patients were offered study enrollment after institutional review board approval. This analysis was limited to 319 unique patients without a prior diagnosis of PCa and pathological evaluation was performed by a variety of pathologists at each institution. Urine (2.5 ml) was transferred to a PROGENSA® urine transport tube (Hologic Inc, San Diego, California). PCA3, T2:ERG and PSA RNA copies were quantified using transcription mediated amplification assays. Target RNAs were purified by hybridization to magnetic particles coated with specific oligonucleotides, amplified and detected using chemiluminescent probes.[11,12] PSA mRNA serves as a prostate specific housekeeping gene to which PCA3 and T2:ERG RNA copy numbers are normalized, ensuring that RNA yield is sufficient. Samples with PSA values of more than 7,000 copies per ml were informative.

Nonparametric Mann-Whitney U tests were performed to compare PCA3 and T2:ERG scores for the entire cohort stratified by race. A model to predict PCa and high grade PCa was created using SOC variables, which included age, self-reported race, family history of PCa, prior biopsy and abnormal DRE, plus serum PSA. PCA3 and T2:ERG scores were then added using the likelihood ratio test of nested models, which tests for a statistical increase from the addition of each biomarker. Each model was built using multiple logistic regressions and performance was reported using concordance statistics (c-statistics). The reported c-statistics were calculated using 1,000 bootstrap samples to correct for overfitting. The models were stratified by race (AA and nonAA) for PCa and high grade PCa. High grade disease was defined as the presence of Gleason 7 or higher prostate cancer. DCA was performed to compare the net benefit of using SOC, plus serum PSA, with PCA3 and T2:ERG.[13] The net benefit is compared to the assumption that all cases are either positive for PCa and should be biopsied vs the assumption that all cases are negative for PCa and should not be biopsied. Therefore, a positive net benefit indicates that it would be better to use the model than to assume all cases are negative for PCa.