Racial Variation in the Utility of Urinary Biomarkers PCA3 and T2ERG in a Large Multicenter Study

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Racial variation in the utility of urinary biomarkers, PCA3 and T2ERG, in a large, multicenter study

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Abstract

Background—It is unknown whether urinary biomarkers for prostate cancer (PCa) have added utility to clinical risk calculators in different racial groups.

Objective—Examine the added utility to clinical risk calculators for urinary biomarkers in prediction of PCa in African American (AA) and non-AA men.

Design—Demographics, Prostate Cancer Prevention Trial (PCPT) risk scores, biomarker data (PCA3 and T2ERG), and biopsy pathology features prospectively collected from 718 men as part of the Early Detection Research Network (EDRN).

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Author contributions: Padraic G O’Malley had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: O’Malley, Lee, Barbieri, Scherr (Race variation) Thompson, Sanda, Rubin, Wei, Scherr (EDRN) Acquisition of data: O’Malley, Thompson, Sanda, Rubin, Wei, Scherr Analysis and interpretation of data: O’Malley, Nguyen, Al Hussein Al Awamlh, Wu, Christos, Lee, Barbieri, Scherr Drafting of the manuscript: O’Malley, Nguyen, Al Awamlh, Wu, Christos Critical revision of the manuscript for important intellectual content: O’Malley, Nguyen, Al Awamlh, Rubin, Barbieri, Scherr Statistical analysis: O’Malley, Wu, Christos Obtaining funding: Thompson, Sanda, Rubin, Scherr Administrative, technical, or material support: Al Hussein Al Awamlh, Barbieri, Rubin Supervision: Barbieri, Scherr
Outcome measures and statistical analysis—Utility determined by generation of receiver operating curves and comparison of area under the curve (AUC) values for the baseline multivariable PCPT model and for models containing biomarker scores.

Results and limitations—PCA3 and T2ERG added utility for prediction of PCa and clinically significant PCa (CS PCa) when combined with PCPT risk calculator. This utility was seen in non-AA men only (PCA3: AUC 0.64 increased to 0.75 for PCa [p<0.001], 0.69 to 0.77 for CS PCa p<0.001; T2ERG: 0.64 to 0.74 for PCa [p<0.001], 0.69 to 0.73 for CS PCa [p=0.029]). AA men did not have added benefit with addition of biomarkers (PCA3: AUC 0.75 to 0.77 [p=0.64], 0.65 to 0.66 [p = 0.74]; T2ERG: 0.75 to 0.74 [p = 0.74], 0.65 to 0.64 [p = 0.88], for PCa and CS PCa, respectively).

Limitations include small number of AA men (n= 72). Post-hoc, sub-group analysis nature limits findings to being hypothesis generating.

Conclusions—As novel biomarkers are discovered, clinical utility should be established across demographically diverse cohorts.

1. INTRODUCTION

Prostate cancer (PCa) screening is the most controversial area in urologic oncology. The risks of over-diagnosis and resultant overtreatment have been well-documented, and the contribution of prostate-specific antigen (PSA) screening in decreasing mortality remains unproven [1]. However, almost 30,000 American men were expected to die from PCa in 2014 [2]. The debate has put the utility of PSA for detection of PCa under scrutiny. Despite its value in clinical practice, PSA has limits as a biomarker, it lacks both specificity and sensitivity in the detection of PCa [3].

Incidence rates of PCa are higher in African American (AA) men compared to all other racial groups [2]. AA men present with more aggressive disease [4] and have the highest PCa-related death rates among ethnic groups [2]. Several factors have been proposed for this racial disparity, including biological factors as well as access to health care [5, 6].

Research has uncovered promising biomarkers in PCa. Among them, Prostate Cancer Antigen 3 (PCA3), and transmembrane protease, serine2 and v-ets erythroblastosis virus E26 oncogene homolog gene fusion (T2ERG) have been utilized to improve prediction models like the Prostate Cancer Prevention Trial Risk Calculator (PCPT RC). The utility of biomarkers in specific racial groups, however, is unknown.

Against the backdrop of well-known racial variations in detection and biology, we evaluated the added utility of urinary PCA3 and/or T2ERG to baseline clinical risk calculator model, the PCPT RC, amongst AA and non-AA men in the EDRN cohort.

2. PATIENTS AND METHODS

2.1. Patient population

733 men were invited to participate in institutional review board approved EDRN study between December 2009 to June 2011 [7, 8]. Participants had to have one or more of the
following indications: elevated/increasing PSA, <15% free PSA, positive family history, prior atypical small acinar proliferation or high-grade prostate intra-epithelial neoplasia, and/or abnormal digital rectal examination (DRE). Men participating in an intervention trial for prostate disease, history of prior prostate surgery, prior saturation or any prostate biopsy within 6 months, and prior exposure to PCA3 testing were excluded. Race was patient self-reported, categorized as AA and non-AA for analysis.

Post-DRE urine was prospectively collected from men presenting for transrectal ultrasound (TRUS) guided biopsy at three EDRN sites (Harvard, University of Michigan, and Weill-Cornell). Fifteen men were excluded for the following: ineligible after consent (prior surgery or biopsy, did not meet other inclusion criteria), inadequate urine sample, uninformative PCA3/T2ERG, no biopsy, missing PCPT RC component, PSA or missing biopsy information, and metastatic disease at presentation. The remaining 718 men had complete demographic, urinary biomarker, and biopsy data. Each site was blinded to biomarker results.

2.2 Specimen Collection and Assays

1. PCA3—Specimens for PCA3 collected after DRE with manipulation and processed as described previously [7]. Ratio of urinary PCA3 to PSA mRNA generated the PCA3 score [9].

2. T2ERG—Urinary T2ERG determined using previously described second-generation TMPRSS2:ERG assay [10]. T2ERG scores calculated as mean urine T2ERG to PSA mRNA.

2.3 Outcome measures

1. Biopsy data—TRUS biopsies performed using standard template. Specimens reviewed at each clinical site. However, 10% of samples randomly selected for independent review by a central pathologist. Gleason grading was according to 2005 International Society of Urologic Pathology Gleason grading system.

2. PCA3 and T2ERG scores—PCA3 and T2ERG scores were treated as continuous variables. T2ERG results underwent log transformation prior to analysis.

3. PCPT RC and CS PCPT RC—The PCPT RC was developed after analysis of men in placebo group of the PCPT [11]. PSA, family history, DRE findings, and history of a prior negative biopsy provided independent predictive value to the calculation of risk of a biopsy that showed presence of cancer. The PCPT RC 1.0 multivariable model R code is publicly available at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp and is still widely in use in practice. PCPT RC in this manuscript refers to the PCPT RC 1.0 relative risk. CS PCPT RC refers to prediction of clinically significant disease defined as Gleason ≥7. Variables contained in the model are as follows: Age, PSA (continuous variables), Race, Family history, DRE, and Prior Biopsy (categorical variables).

Each patient’s variables were inputted into the published regression model, PCPT RC 1.0, which gave risk estimates for individual patients for PCa and CS PCa.
2.4 Statistical analysis

Primary outcome was presence of any PCa or CS PCa. For continuous variables, mean (± standard deviation) or median (interquartile range) were compared between sub-groups using two-sample t-test or Mann-Whitney U test, respectively. For categorical variables, proportions were compared between groups using chi-square test or Kruskal-Wallis testing.

Receiver operating characteristic curves (ROC) were generated for each group to compare predictive performance of PCPT RC (base model) and with PCA3 and/or T2ERG via logistic regression models. The area under the curve (AUC) method was used to compare the base model of PCPT RC-alone with models including PCA3 and/or T2ERG, in the two groups. Similar analyses were performed for CS PCa utilizing CS PCPT RC. AUCs were compared by the DeLong method. Power estimation was performed, using an alpha of 0.05 and population size of 72 for AA men, to determine if there existed sufficient power to detect a 10% variation in AUC after addition of the biomarkers to the PCPT RC. Analyses performed with Stata v14.0 (StataCorp, TX).

3. RESULTS

Demographics, Urinary Biomarkers, and Risk Calculators

646 of 718 men (90%) were non-AA and 72 (10%) were AA. Table 1 delineates pre-biopsy serum PSA and prognostic scores among the sub-groups. PCA3 and T2ERG are further stratified by presence or absence of PCa on biopsy. There were significantly higher PCA3, PCPT RC and CS PCPT RC scores for AA versus non-AA men (p <0.001, 0.041, <0.001, respectively). T2ERG scores were higher in non-AA men but was not significant (p=0.200). Higher PCA3 and T2ERG scores were seen in patients with positive biopsy (PCA3: p<0.001; T2ERG: p<0.001). Furthermore, non-AA men had higher T2ERG than AA men in those men with positive biopsies (p=0.015). Conversely, AA men had higher PCA3 levels in patients with negative biopsy (p=0.011) but not significantly in those with positive biopsy (0.282) versus non-AA men.

Biopsy Pathology

On biopsy, 324 (45%) and 194 (27%) men were found to have PCa and CS PCa, respectively. AA men were not found to have significantly higher rate of PCa or CS PCa (p=0.104; p=0.121 respectively). The median total number of cores and of positive cores was not different between groups (Table 2). The distribution of Gleason scores did not differ between AA and non-AA men (0.952).

PCPT RC and Biomarkers

ROC curves for the models are shown in Figure 1 for both groups. ROC curves generated AUC values for baseline PCPT RC with or without urinary biomarkers (Table 3). PCA3 demonstrated added utility in non-AA men, with increase in the AUC. Amongst AA men, however, there was no significant increase in AUC (Figure 1a, Table 3). Addition of T2ERG to PCPT RC failed to demonstrate significant added utility in AA men but was significantly improved amongst non-AA (Figure 1b, Table 3). The combination of PCA3 and T2ERG also demonstrated added utility in non-AA (Figure 1c, Table 3). The addition of PCA3 and
T2ERG combined, when compared to the addition of PCA3 or T2ERG alone showed a significant improved detection ability in non-AA men (p<0.001 for both). The combination of both urinary biomarkers to the PCPT RC failed to show added utility over baseline PCPT RC in AA men.

**CS PCPT RC and Biomarkers**

Figure 2 demonstrates ROC curves for CS PCPT RC with addition of PCA3, T2ERG, or both. AUCs for models for sub-groups are presented in Table 4. PCA3 (Figure 2a), T2ERG (Figure 2b), and combination (Figure 2c) demonstrated added utility above baseline risk calculator, CS PCPT RC in this case, in non-AA men but failed to show benefit in AA men. Additionally, combination of PCA3 and T2 ERG was better at improving CS PCa detection than T2ERG alone was in non-AA men (p<0.001). There was no significant improvement in using both biomarkers versus PCA3 for CS PCa in non-AA men (p = 0.073).

**4. DISCUSSION**

Biomarkers are quantifiable measures of a cellular or molecular alteration which may be involved in biological pathways. They have shown potential to assist in screening, diagnosis, prognosticating, and monitoring response to treatment [12]. This study examines the added utility of two urinary biomarkers, PCA3 and T2ERG, to a commonly used clinical risk calculator for prediction of PCa on biopsy. Our results show that the addition of PCA3 and T2ERG alone or in combination enhances the performance of both the PCPT RC and the CS PCPT RC in non-AA men. However, no model including biomarkers showed added utility in AA men in this cohort.

A number of studies have examined the utility of the PCPT RC in various cohorts. In 2011, Nam et al., evaluated the PCPT RC in concert with their own risk calculator in a prospective validation study [13]. They generated AUC values of 0.61 (95% CI 0.59 – 0.64) for the PCPT RC model, while their own risk calculator developed at Sunnybrook Health Sciences Center gave an AUC of 0.67 (95% CI 0.65 – 0.69) and was found to be superior on decision curve analysis across thresholds [13]. Although the number of AA men comprised only 5% of their study population, there was a significant OR of 3.3 (95% CI 1.9 – 5.7) associated with AA race. Of note the rate of biopsy positivity was high, similar to this cohort from the EDRN, at approximately 40%. In the external validation study of PCPT in the San Antonio Center of Biomarkers of Risk of Prostate Cancer (SABOR) the rate of positive biopsy amongst AA men was 49% [14]. Although the rate of positive biopsies in the PCPT trial was lower (22%), it should be noted that only a small portion of men were African American (3.2%) and inclusion criteria required normal DRE and PSA ≤3 ng/ml [11]. Evaluation of PCPT RC in ten international cohorts showed improved predictive ability of the calculator in the majority of cohorts [15]. However, there was a wide discrepancy of AUC values generated and validity was questionable in several of the cohorts. Of note only three of the cohorts contained AA men: the Cleveland Clinic, SABOR, and Durham VA. In the SABOR and Durham VA cohorts the calculator was found to be well calibrated [15]. Indeed in the SABOR cohort they demonstrated a higher AUC value for AA men of 0.80 (95% CI 0.68–
0.92) compared to non-AA men 0.66 (95% CI 0.61–0.71) [14]. This may reflect a lack of general applicability of PCPT RC to varying populations.

Several studies have shown racial variations in both expression of biomarkers in PCa and in PCa genome-wide association studies [16, 17]. Current biomarkers which have been evaluated in larger series of men with or suspected of having PCa have had varied results. However none of these studies have examined the racial variation that may exist for individual biomarkers and how it impacts clinical utility.

PCA3 is a non-coding RNA found to be over-expressed in PCa tissue [18]. PCA3 is detectable in the urine of men with PCa and is not influenced by factors such as prostate size and serum PSA level, a limitation of other biomarkers such as -2proPSA [19–22]. Most recently the EDRN study of PCA3 demonstrated utility of PCA3 score higher than 60 for predicting an initial positive biopsy [9]. This study involved 13% AA from multiple centers. Recent data has suggested added utility of PCA3 to clinical tools such as European Randomized Study of Screening for Prostate Cancer (ERSPC) multivariable prediction model [23]. Furthermore, several studies have shown the ability of urinary biomarkers such as PCA3 and T2ERG to improve sensitivity and specificity for screening for PCa [9, 23, 24].

This study is the first investigation of contemporary, validated biomarkers for PCa in racial sub-groups. Similar to other studies, PCA3 has added predictive utility to a baseline clinical risk calculator. This was seen in non-AA men for both PCa and CS PCa. However, amongst AA men, almost no change to the model was seen for PCa or CS PCa, although the baseline model has shown higher predictive value. Similarly, urinary T2ERG was found to add significant value in non-AA men but not AA men for PCa or CS PCa. The combination of the biomarkers again appeared to have utility in non-AA men alone. Furthermore, there was significant improvement when comparing the addition of PCA3 or T2ERG alone versus the combination of both biomarkers.

Urinary T2ERG has been evaluated as a biomarker both for prediction of PCa on biopsy [25, 26] and for baseline analysis in an active surveillance cohort [27]. These studies found a benefit to T2ERG. The most recent evidence for urinary T2ERG comes from the study which clearly demonstrated clinical utility in the EDRN training cohort and validated this finding in an independent cohort [8]. Our findings, also the EDRN training cohort, in non-AA men are similar to their findings, and is reassuring.

Two recent small studies examined non-validated novel PCa biomarkers. There appeared to be utility in AA men as well as Caucasian men for the Genomic Evaluators of Metastatic Prostate Cancer (GEMCaP) for prediction of biochemical disease, however there was no benefit detected with ABCD3 gene expression for prediction of metastatic disease in AA men [28, 29]. Clearly given the drive for precision medicine, novel and cancer-specific biomarkers, and improved risk stratification for detection and management, it is important to remain cognizant that racial variations can and do exist [5, 6, 16, 17]. The one strategy, may not fit all, i.e. AA men who are known to have biological disease variability. Further assessment of other available biomarkers, such as phi, and investigation of MRI for detection.
of anterior tumors may be more useful in African American men. Indeed, our findings serve as further impetus for true personalization in medicine.

The current study has several limitations. Men were followed only through index biopsy, and thus if biopsy was a false negative, which is a known distinct possibility, we did not have a means of capturing subsequent results. Although there is reasonable representation of AA men, the numbers are still low. The study was adequately powered to detect a 10% significant difference in predictive utility with the addition of biomarkers. Most importantly, this study is limited by the post hoc nature and sub-group analysis and thus conclusions drawn can only be considered hypothesis generating. Lastly, the detection rate of PCa on biopsy in AA may be underestimated due to higher prevalence of anterior tumors and inherent under sampling of these [30] and furthermore, PCA3 and T2ERG may not be accurate biomarkers for these lesions.

CONCLUSION

This study highlights important points. PCA3 and T2ERG add predictive value for detection of PCa and CS PCa in non-AA men. Second, PCA3 and T2ERG were not detected to add predictive value for PCa in AA men. Further validation of the hypothesis that the clinical utility of these biomarkers is restricted to specific racial subgroups is needed with large well annotated cohorts.

Acknowledgments

We would like to thank Dr. Scott Tomlins for valuable insight into urinary T2ERG and optimization of their interpretation.

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Key of Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>PCa</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>CS PCa</td>
<td>Clinically significant Prostate cancer</td>
</tr>
<tr>
<td>EDRN</td>
<td>Early Detection Research Network</td>
</tr>
<tr>
<td>AA</td>
<td>African American</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>PCA3</td>
<td>Prostate Cancer Antigen 3</td>
</tr>
<tr>
<td>T2ERG</td>
<td>Transmembrane protease serine 2 and v-ets erythroblastosis virus E26 oncogene homolog gene fusion</td>
</tr>
</tbody>
</table>
PCPT RC  Prostate Cancer Prevention Trial Risk Calculator
DRE  Digital rectal exam
ROC  Receiver operating characteristic
AUC  Area under the curve
ERSPC  European Randomized Study of Screening for Prostate Cancer

References


Figure 1. Predictive ability of PCPT RC and urinary biomarkers, PCA3 and T2ERG in racial subgroups to predict prostate cancer on biopsy
Left panels: non-AA. Right Panels: AA. Predictive ability to detect prostate cancer of multivariable model PCPT RC (Blue) and with model and biomarker (Red). (A) Addition of PCA3 to multivariable model PCPT RC score; (B) Addition of T2ERG; (C) Addition of PCA3 and T2ERG.
Figure 2. Predictive ability of CS PCPT RC and urinary biomarkers, PCA3 and T2ERG in racial subgroups to predict clinically significant prostate cancer

Left panels: non-AA. Right Panels: AA. Predictive ability to detect prostate cancer of multivariable model CS PCPT RC (Blue) and with model and biomarker (Red). (A) Addition of PCA3 to multivariable model PCPT RC score; (B) Addition of T2ERG; (C) Addition of PCA3 and T2ERG.
Table 1
Baseline demographics, PSA, urinary biomarker and PCPT RC scores for racial sub-groups in the EDRN cohort.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 718)</th>
<th>Non-AA (n = 646)</th>
<th>AA (n = 72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median, IQR)</td>
<td>63 (57–68)</td>
<td>63 (58–68)</td>
<td>63 (53–69)</td>
<td>0.36</td>
</tr>
<tr>
<td>EDRN Site:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornell</td>
<td>317</td>
<td>290 (91.5%)</td>
<td>27 (8.5%)</td>
<td></td>
</tr>
<tr>
<td>Harvard</td>
<td>113</td>
<td>100 (88.5%)</td>
<td>13 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Michigan</td>
<td>288</td>
<td>256 (88.9%)</td>
<td>32 (11.1%)</td>
<td>–</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Median, IQR)</td>
<td>5.1 (3.8–7.0)</td>
<td>5 (3.8–6.9)</td>
<td>5.84 (4.15–8.21)</td>
<td>0.058</td>
</tr>
<tr>
<td>PCA3 (Median, IQR)</td>
<td>24.6 (11.6–52.2)</td>
<td>23.5 (11.2–50.8)</td>
<td>37.7 (17.7–69.6)</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Benign</td>
<td>14.7 (8.8–30.1)</td>
<td>14.8 (8.4–28.9)</td>
<td>17.4 (10.5–50.4)</td>
<td><strong>0.011</strong></td>
</tr>
<tr>
<td>PCa</td>
<td>42.5 (20.3–74.1)</td>
<td>&lt;0.001</td>
<td>40 (19.2–73.6)</td>
<td>54 (33.1–84.2)</td>
</tr>
<tr>
<td>T2ERG (Median, IQR)</td>
<td>1.92 (0–3.75)</td>
<td>2.00 (0–3.78)</td>
<td>1.10 (0–3.44)</td>
<td>0.20</td>
</tr>
<tr>
<td>(Median, IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>0.59 (0–2.77)</td>
<td>0.59 (0–2.77)</td>
<td>0.83 (0–2.30)</td>
<td>0.95</td>
</tr>
<tr>
<td>PCa</td>
<td>3.13 (0.69–4.48)</td>
<td>&lt;0.001</td>
<td>3.34 (1.10–4.55)</td>
<td>1.81 (0–3.63)</td>
</tr>
<tr>
<td>PCPT RC (Median, IQR)</td>
<td>40.2 (33.5–48.1)</td>
<td>39.8 (33.5–47.9)</td>
<td>43.1 (36.7–50.2)</td>
<td><strong>0.041</strong></td>
</tr>
<tr>
<td>CS PCPT RC (Median, IQR)</td>
<td>10.1 (6.7–17.5)</td>
<td>9.4 (6.5–14.8)</td>
<td>24.9 (17.5–37.2)</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
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</table>
Table 2

EDRN cohort sub-groups pathology characteristics on transrectal ultrasound guided biopsy.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 718)</th>
<th>Non-AA (n = 646)</th>
<th>AA (n = 72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy (+)</td>
<td>324 (45.1%)</td>
<td>285 (44%)</td>
<td>39 (54.2%)</td>
<td>0.104</td>
</tr>
<tr>
<td>Biopsy (+) CS</td>
<td>194 (27.0%)</td>
<td>169 (26.2%)</td>
<td>25 (34.7%)</td>
<td>0.121</td>
</tr>
<tr>
<td>No. Biopsy Core</td>
<td>12 (12–16)</td>
<td>12 (12–16)</td>
<td>12 (12–15)</td>
<td>0.295</td>
</tr>
<tr>
<td>(Median, IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (+) Biopsy Core (Median, IQR)</td>
<td>3 (2–6)</td>
<td>3 (2–6)</td>
<td>5 (2–7)</td>
<td>0.081</td>
</tr>
<tr>
<td>Gleason Score:</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>130 (40.1%)</td>
<td>116 (40.7%)</td>
<td>14 (35.9%)</td>
<td>0.952</td>
</tr>
<tr>
<td>7</td>
<td>148 (45.7%)</td>
<td>126 (44.2%)</td>
<td>22 (56.4%)</td>
<td></td>
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<tr>
<td>8</td>
<td>22 (6.8%)</td>
<td>20 (7.0%)</td>
<td>2 (5.1%)</td>
<td></td>
</tr>
<tr>
<td>9–10</td>
<td>24 (7.4%)</td>
<td>23 (8.1%)</td>
<td>1 (2.6%)</td>
<td></td>
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</tbody>
</table>
Table 3

AUC values for the various models including PCA3, T2ERG or both in addition to the PCPT RC for non-AA and AA men for the detection of Prostate cancer.

<table>
<thead>
<tr>
<th>Model</th>
<th>Non-AA Men</th>
<th>AA Men</th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>AUC [95% CI]</td>
<td>p value</td>
<td>AUC [95% CI]</td>
<td>p value</td>
</tr>
<tr>
<td>PCPT RC</td>
<td>0.64 [0.60–0.68]</td>
<td>–</td>
<td>0.75 [0.63–0.87]</td>
<td>–</td>
</tr>
<tr>
<td>PCPT RC + PCA3</td>
<td>0.75 [0.71–0.79]</td>
<td>&lt;0.001</td>
<td>0.77 [0.65–0.88]</td>
<td>0.64</td>
</tr>
<tr>
<td>PCPT RC + T2ERG</td>
<td>0.74 [0.70–0.78]</td>
<td>&lt;0.001</td>
<td>0.74 [0.62–0.86]</td>
<td>0.74</td>
</tr>
<tr>
<td>PCPT RC + PCA3 + T2ERG†</td>
<td>0.79 [0.75–0.82]</td>
<td>&lt;0.001</td>
<td>0.77 [0.65–0.88]</td>
<td>0.635</td>
</tr>
</tbody>
</table>

†PCPT RC + PCA3 + T2ERG compared to PCPT RC + PCA3 or PCPT RC + T2ERG p<0.001 for both
### Table 4

AUC values for the various models including PCA3, T2ERG or both in addition to the CS PCPT RC for non-AA and AA men for the detection of clinically significant Prostate cancer.

<table>
<thead>
<tr>
<th>Model</th>
<th>Non-AA men</th>
<th>AA men</th>
<th>p value</th>
<th>Non-AA men</th>
<th>AA men</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS PCPT</td>
<td>0.69 [0.64–0.73]</td>
<td>0.65 [0.52–0.77]</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS PCPT + PCA3</td>
<td>0.77 [0.73–0.81]</td>
<td>0.66 [0.53–0.79]</td>
<td><strong>&lt;0.001</strong></td>
<td>0.736</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS PCPT + T2ERG</td>
<td>0.73 [0.69–0.78]</td>
<td>0.64 [0.51–0.77]</td>
<td><strong>0.029</strong></td>
<td>0.880</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS PCPT + PCA3 + T2ERG‡</td>
<td>0.79 [0.75–0.83]</td>
<td>0.67 [0.54–0.80]</td>
<td><strong>&lt;0.001</strong></td>
<td>0.714</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

‡PCPT RC + PCA3 + T2ERG compared to PCPT RC + PCA3 (p=0.073) or PCPT RC + T2ERG (p<0.001)