Prostate Cancer Gene 3 Score Predicts Prostate Biopsy Outcome in Men Receiving Dutasteride for Prevention of Prostate Cancer: Results From the REDUCE Trial

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OBJECTIVES To examine the ability of the urinary prostate cancer gene 3 (PCA3) assay to predict biopsy-detected cancers in men receiving dutasteride in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study cohort.

METHODS Urine and serum samples from 930 men in the active arm were acquired at years 2 and 4 of the biopsy visits. In addition to univariate logistic regression and receiver operating characteristic analysis, multivariate analysis for association with biopsy outcome was performed for PCA3 score in the presence of serum prostate-specific antigen (PSA), age, prostate volume, and family history of prostate cancer.

RESULTS At year 2, the univariate PCA3 score area under the receiver operating characteristic curve (AUC) was 0.668 versus 0.603 for PSA. At year 4, the PCA3 assay significantly predicted the biopsy outcome (AUC 0.628, 95% confidence interval 0.556-0.700), and the PSA level was not predictive (AUC 0.556, 95% confidence interval 0.469-0.642). The year 2 multivariate model yielded an AUC of 0.712. Removing the PCA3 score decreased the AUC to 0.660 ($P = .0166$ vs the full model). The median PCA3 scores in the dutasteride arm were not different from those in the 1072 men in the placebo arm (16.2 and 17.2 at year 2, $P = .1755$; and 18.8 and 18.1 at year 4, $P = .2340$, respectively). However, the PSA values were reduced >50% in the dutasteride arm at both visits (both $P < .0001$ vs placebo). At a PCA3 score cutoff of 35, the sensitivity and specificity were equivalent between the 2 arms.

CONCLUSIONS In the present study, the PCA3 assay outperformed PSA for cancer detection in men undergoing dutasteride treatment and improved the diagnostic accuracy when combined with the PSA level and other clinical variables. In addition, no adjustment in PCA3 score was needed to yield equivalent clinical performance between the dutasteride and placebo arms. These findings are particularly important in light of the potential role of dutasteride for prostate cancer chemoprevention. UROLOGY 78: 380–385, 2011. © 2011 Elsevier Inc.

Prostate cancer gene 3 (PCA3), a marker highly overexpressed in prostate cancer cells compared with the levels in benign prostatic tissue,[1,2] has been measured in urine after digital rectal examination in men at risk of prostate cancer (PCa).[3-5] Elevated PCA3 scores have been associated with a positive biopsy outcome,[4-7] and the performance of the PCA3 assay is maintained through the first and subsequent biopsies.[6,7] The PCA3 scores have also been correlated with the disease severity, according to the tumor volume measurements,[8] tumor grade,[6] and Gleason score[8,9] evaluations. Multiple studies have also compared the performance of the PCA3 assay to that of the traditional serum prostate-specific antigen (PSA) and percentage of free PSA measurements. These studies have demonstrated greater associations for the PCA3 score with the biopsy outcome versus the traditional markers,[4,5] as well as independence of the PCA3 score from these markers and other clinical variables.[6,8,9] Thus, the PCA3 score has emerged as a promising marker of PCa risk that practitioners can incorporate into biopsy decision-making protocols.

To date, all clinical studies of the PCA3 assay have excluded men taking 5α-reductase inhibitors (5-ARIs). The exclusions were primarily determined by the known diminution of the PSA values[10] during treatment with 5-ARIs and the unknown effects on the PCA3 assay.

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However, because these compounds are in widespread use in men with benign prostatic hyperplasia, the question arises as to whether the performance of the PCA3 assay extends to the population of men taking these drugs for benign prostatic hyperplasia, because they could also undergo evaluation for PCa. To date, only a single small study has investigated the effect of a 5-ARI on the PCA3 assay.[11]

Additionally, 5-ARIs could further penetrate the population at risk of prostatic disease according to recent PCa chemoprevention studies. The worldwide REduction by DUtasteride of prostate Cancer Events (REDUCE) trial[12] demonstrated that dutasteride, a dual (type 1 and 2) 5-ARI, reduced the risk of PCa by 23% during the 4-year study period.[13] The size and design of the study presents an opportunity to study the performance of the PCA3 assay in men treated with a 5-ARI. Thus, the objective of the present investigation was to examine the ability of the PCA3 assay to predict biopsy-detected PCa in men receiving dutasteride in the REDUCE study cohort.

MATERIAL AND METHODS

Study Population

The REDUCE trial was an international, multicenter, double-blind, placebo-controlled chemoprevention study designed to determine whether dutasteride administered at 0.5 mg/d decreased the risk of biopsy-detectable PCa during a 4-year period. The study enrolled 8122 men (4049 and 4073 in the dutasteride and placebo arms, respectively) with a prostate volume $\leq$80 cm^3 and aged 50-75 years. The men aged <60 years were required to have a recent serum PSA level of 2.5-10 ng/mL, and the men aged $\geq$60 years were required to have PSA level of 3-10 ng/mL. In addition, men had to have had a single previous prostate biopsy (within 6 months of enrollment) of 6-12 cores without evidence of cancer, high-grade prostatic intraepithelial neoplasia, or atypical small acinar proliferation. After enrollment, the study subjects were followed up for the 4-year study period with clinical evaluations, laboratory sampling, and 10-core biopsies performed at 2 and 4 years. Throughout the study period, a total of 1517 PCa were observed (n = 659 and n = 858 in the dutasteride and placebo arms, respectively).

Urinary Sampling and PCA3 Measurement

Urine samples for PCA3 analysis were obtained before the year 2 and year 4 biopsies from the subsets of subjects in the dutasteride (n = 930) and placebo (n = 1072) arms of the study. Urine samples were not collected at study baseline or at the time of "for cause" biopsies. The REDUCE trial sites that were able to collect and process postdigital rectal examination urine samples were included in the present substudy; no other site selection criteria were used.

The investigators were instructed to perform a digital rectal examination of 3 strokes per prostate lobe. Each subject then provided 20-30 mL of urine in a first catch specimen. The urine samples were maintained on ice and processed within approximately 4 hours of collection. Whole urine samples were mixed with equal volumes of Gen-Probe urine Transport Medium to lyse shed prostate cells and stabilize the RNA. The stabilized samples were frozen at −70°C and then batch shipped on dry ice to an independent testing laboratory (Caris Life Sciences/Molecular Profiling Institute, Phoenix, AZ).

The assay for quantification of PCA3 and PSA mRNA levels has been previously described.[4] The PCA3 score is calculated as the ratio of the PCA3 mRNA copies to PSA mRNA copies × 1000. Informative specimens are defined as having enough RNA for accurate quantification of a PCA3 score based on PSA mRNA greater than the lowest positive calibrator (~7500 copies/mL). The assay has been reported to exhibit sufficient sensitivity and specificity for the detection of the PCA3 and PSA mRNA with a >94% informative rate of specimens, and an intra-assay, interassay, and intersite imprecision of <14%, <10%, and <10%, respectively, for mRNA.[14]

Statistical Analysis

For analysis of the serum PSA levels and clinical performance, the last serum PSA value obtained before biopsy was used. The values for the PCA3 scores and PSA levels between the dutasteride and placebo arms were compared using the Wilcoxon rank sum test. The same test was used to examine the significance of differences in marker values from the subjects with biopsy-detected PCa and with no detected PCa in the dutasteride arm. The sensitivity and specificity and their associated 95% confidence intervals (CIs) for the detection of PCa were determined for the PCA3 assay at various cutpoints using the receiver operating characteristic (ROC) analysis and the areas under the curve (AUC) compared between the PCA3 score and PSA level using the method of DeLong et al.[15] Univariate logistic regression analysis for the association of PCA3 scores and PSA levels with the biopsy outcome was also performed. Odds ratios (ORs) and their 95% CIs were determined, in addition to the Wald P value for each term. To evaluate the independence of the PCA3 score in the presence of the PSA level and traditional risk factors, including the prostate volume, patient age, and family history of PCa, multivariate logistic regression models expressing the PCA3 score as a continuous variable were developed. In addition, the AUCs of the models as a whole were determined using ROC analysis. The models were subsequently rerun after exclusion of either the PCA3 score or the PSA level to determine the effect of each variable on the predictive power of the other. Finally, the performance of the full multivariate model using the PCA3 score as a continuous variable was compared to the univariate expression of the PCA3 score and PSA level. For all the foregoing analyses, determinations were made using data available at both the year 2 and year 4 study visits.

The NCSS 2004 (NSCC, Kaysville, UT), JMP, version 5.01 (SAS Institute, Cary, NC), and Analyze-It, version 2.07 (Analyze-It Software, Leeds, UK) software packages were used for the statistical investigations. All tests were 2-tailed, and $P <$ .05 was considered significant.

RESULTS

Subject Characteristics

The subject characteristics at baseline in the 2 study arms are listed in eTable 1. The median serum PSA value was 5.3 and 5.4 ng/mL and the median prostate volume was 43.5 and 44.0 cm^3 for the dutasteride and placebo arms, respectively. A family history of prostate cancer was reported by 15.1% of the subjects in the dutasteride arm

Table 1. Median values and mRNA copies for PCA3 and serum PSA

Variable	Year 2	Year 4
PCA3 score		
Placebo	17.2	18.1
Dutasteride	16.2	18.8
P value	.1755	.2340
Serum PSA (ng/mL)		
Placebo	5.4	5.9
Dutasteride	2.2	2.0
P value	<.0001	<.0001
PCA3 mRNA (copies/mL)		
Placebo	3,845	4,036
Dutasteride	1,475	1,769
PSA mRNA (copies/mL)		
Placebo	228,642	244,337
Dutasteride	96,703	97,212

PCA3, prostate cancer gene 3; PSA, prostate-specific antigen.

and 13.8% in the placebo arm. The median age of the subjects in both study arms was 62 years. The distribution of these variables was not significantly different between the dutasteride and placebo arms (all $P > .05$). In the dutasteride arm, PCA3 scores were available from 649 and 659 subjects at years 2 and 4, respectively (eTable 2). In these subjects, the median prostate volume was nearly identical (~36 cm^3). Across the 2-year period, the percentage of PCa diminished markedly from 13.4% (n = 87) at year 2 to 7.9% (n = 52) at year 4. The Gleason score of these PCa cases were not particularly different, with ~60% and ~30% of the PCa cases with a Gleason score of 6 and 7, respectively, at both points (chi-square, $P = .6057$ across all Gleason scores between the 2 follow-up points). Across the 2 study arms, 89.8% of subjects were white, 7.5% Hispanic, 1.7% black, and 1.0% Asian. The marked skewing toward white subjects precluded investigation of race as a suitable covariate in additional analyses, including the logistic regression models.

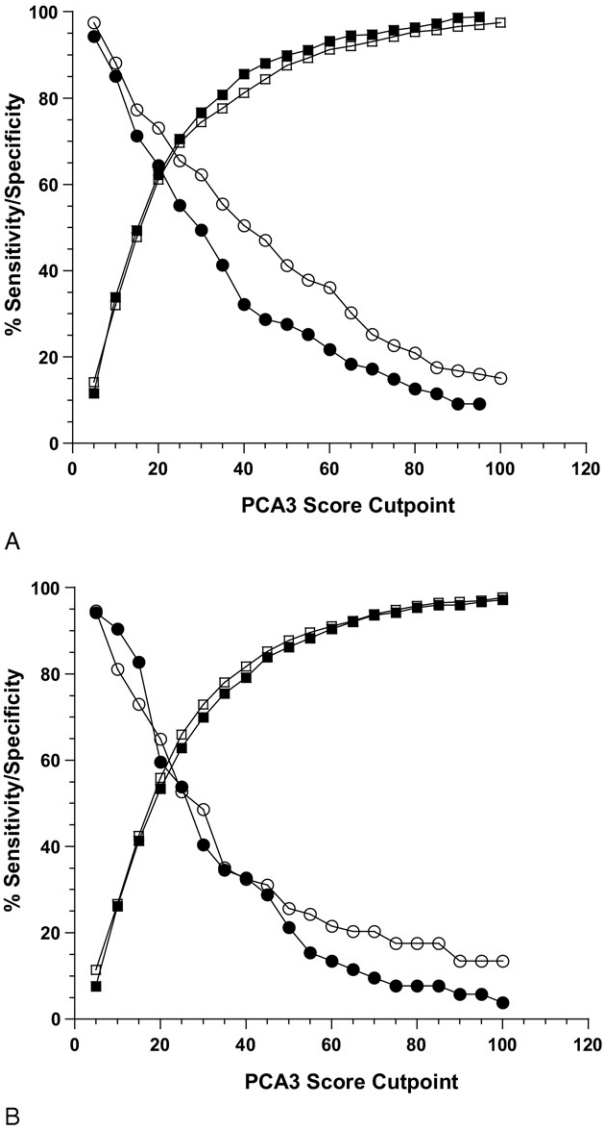

Figure 1. Sensitivity and specificity in dutasteride (black circles, sensitivity; black squares, specificity) and placebo arm (white circles, sensitivity; white squares, specificity) at **(A)** year 2 and **(B)** year 4.

Comparisons Between Dutasteride and Placebo Arms

At years 2 and 4, the median serum PSA values declined by 59% and 66%, respectively, in the dutasteride arm compared with the placebo arm (both $P < .0001$; Table 1). In contrast, the median PCA3 scores were equivalent in the dutasteride and placebo arms. However, the median PCA3 and PSA mRNA levels (copies/mL) were consistently more than twofold lower in the dutasteride arm compared with the placebo arm (Table 1). Although the calculated PCA3 score (PCA3/PSA copies/mL × 1000) remained consistent between the study arms, the decrease in mRNA concentrations reduced the specimen informative rate (ie, percentage of specimens with PSA mRNA level >7500 copies/mL) from 94% at both years 2 and 4 in the placebo arm to 79% and 78% in the same years in the dutasteride arm. If the threshold level for PSA mRNA were reduced from 7500 copies/mL to 1000 copies/mL, the informative rates in the dutasteride arm would be increased to 94% and 95% at years 2 and 4, respectively, with no effect on the PCA3 assay clinical performance for predicting biopsy outcome (data not shown).

The sensitivity and specificity for the prediction of the prostate biopsy outcome were determined at various PCA3 score cutpoints using ROC analysis. Figure 1 displays the sensitivity and specificity curves at years 2 and 4 for the dutasteride and placebo arms. For both points, the specificity curves were nearly identical, indicating no difference in the specificity for the detection of PCa. However, at year 2, the sensitivity curves diverged at cutpoints >15. At the cutpoint most often viewed as optimal for the PCA3 assay, a score of 35, the sensitivity point estimate and 95% CI for the dutasteride and pla-

Table 2. Multivariate logistic regression models for association of PCA3 and other variables with biopsy-detected prostate cancer in dutasteride arm

Variable	OR	95% CI	*P* Value	Model AUC	*P* Value vs Full Model AUC When Excluding PCA3
Multivariate logistic regression model 1—PCA3 score as continuous variable at year 2					
Age (y)	1.0469	1.00-1.09	.0327	0.712	.0166*
Family history (yes vs no)	1.9470	1.05-3.60	.0336		
PCA3 score	1.0184	1.01-1.03	<.0001		
Prostate volume (cm^3)	0.9759	0.96-0.99	.0064		
Serum PSA (ng/mL)	1.2211	1.07-1.39	.0026		
Multivariate logistic regression model 2—PCA3 score as continuous variable at year 4					
Age (y)	0.9788	0.93-1.03	.4106	0.636	.0900†
Family history (yes vs no)	1.2603	0.57-2.77	.5643		
PCA3 score	1.0102	1.00-1.02	.0037		
Prostate volume (cm^3)	0.9746	0.95-0.99	.0136		
Serum PSA (ng/mL)	1.3075	1.11-1.53	.0010		

OR, odds ratio; CI, confidence interval; AUC, area under the receiver operating characteristic curve; other abbreviations as in Table 1.
* AUC for model excluding PCA3 = 0.660.
† AUC for model excluding PCA3 = 0.599.

cebo arms was 41.4% (95% CI 30.9%-52.4%) and 55.5% (95% CI 46.1%-74.6%), respectively. The overlap in the 95% CIs indicates that the visual divergence was not significant at this cutpoint. The 95% CIs of sensitivity for all cutpoints across the range overlapped between the study arms (data not shown). At year 4, the sensitivity began to diverge only at greater cutpoints. At a cutpoint of 35, the point estimates and 95% CIs for the dutasteride and placebo arms were in close agreement at 34.6% (95% CI 22.0%-49.1%) and 35.1% (95% CI 24.4%-47.1%), respectively. Even at the greater cutpoints, the 95% CIs overlapped between the study arms, again indicating that any visual differences were not statistically significant.

PCA3 Assay Performance in Dutasteride Arm Alone and With Covariates

In the dutasteride arm, the PCA3 score, expressed as a continuous variable for the prediction of biopsy outcome, was evaluated using univariate logistic regression analysis and ROC compared with to the serum PSA level. At year 2, the continuous expression of the PCA3 score provided an AUC of 0.668 (95% CI 0.604-0.731). However, this AUC was not significantly differentiated from the PSA AUC of 0.603 (95% CI 0.538-0.668, $P = .1415$). The univariate OR for PCA3 was 1.0174 (95% CI 1.01-1.02) vs 1.1901 (95% CI 1.05-1.35) for PSA. At year 4, the continuous expression of the PCA3 score was a significant predictor of the biopsy result with an AUC of 0.628 (95% CI 0.556-0.700). The AUC for PSA was 0.556 (95% CI 0.469-0.642), indicating an insignificant association with the biopsy result.

Multivariate analysis was performed to characterize the contribution of the PCA3 score to the prediction of the biopsy outcome with traditional variables. Model 1 (Table 2) included the PCA3 score expressed as a continuous variable, serum PSA level, age, prostate volume, and family history of PCa (all year 2 data). All terms in this model were significant predictors, and the PCA3 score provided an OR of 1.0184 (95% CI 1.01-1.03). The ROC-AUC of the full model was 0.712. Removing the PCA3 score from the model resulted in a significant decrease in performance (AUC 0.660, $P = .0166$). In contrast, if the PSA level was excluded from the full model, an insignificant decrease in performance was observed (AUC 0.690, $P = .0649$). Removal of the PSA level only minutely altered the PCA3 score OR from 1.0184 to 1.0185. Similarly, removal of the PCA3 score only marginally altered the PSA OR from 1.2211 to 1.2308. In addition, an insignificant difference was seen when comparing the full model AUC to the PCA3 score (AUC 0.668, $P = .0687$), and a significant difference was seen compared with PSA (AUC 0.603, $P = .0041$; Fig. 2). Thus, the foregoing results have demonstrated that the 2 variables provide complementary information in the multivariate model, but the overall predictive power of the model was driven primarily and independently by the PCA3 score.

At year 4, the PCA3 score as a continuous variable (Table 2) retained its significance, but removal of the term from the model reduced the AUC to a lesser extent than year 2 from 0.636 to 0.599, which did not reach significance ($P = .0900$). The performance of the PCA3 score to predict high-grade PCa (Gleason score ≥7) was also assessed at years 2 and year 4 using univariate logistic regression analysis. At years 2 and 4, 33 and 18 subjects had high-grade PCa, respectively. The PCA3 score as a continuous variable was predictive of high-grade PCa at year 2 (OR 1.0170, 95% CI 1.01-1.03, $P = .0003$) and also at year 4 (OR 1.0112, 95% CI 1.00-1.02, $P = .0380$).

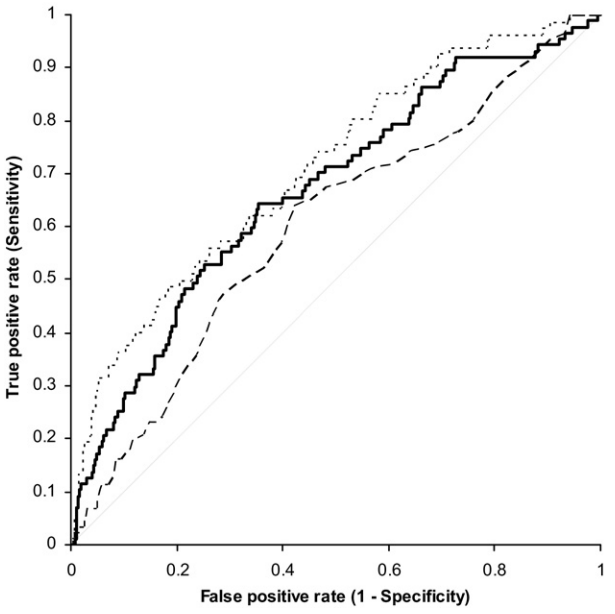

Figure 2. ROC curve analysis for multivariate logistic model (includes PCA3 as continuous variable, serum PSA level, prostate volume, age, and family history of PCa) (dotted line) compared with univariate PCA3 (continuous; solid line, and PSA level (dashed line) at year 2.

However, these results should be viewed in light of the limited numbers of high-grade PCa cases at both periods.

COMMENT

The present study addressed a key unanswered question regarding the clinical utility of the PCA3 assay: whether the PCA3 score could be used to predict biopsy-detectable PCa in men undergoing long-term treatment with dutasteride. Although an overall decrease in both PCA3 mRNA and PSA mRNA values was observed in the dutasteride arm, the median PCA3 scores in the dutasteride and placebo arms were equivalent for ≤4 years of follow-up. The decrease in urine PCA3 and PSA mRNA levels most likely resulted from downregulation of expression by dutasteride, because both genes are regulated by androgens.[16-18] That the PCA3 score is a ratio of the 2 mRNA levels might compensate for the change in expression levels. In contrast, the median serum PSA values were ~50% lower in the treatment than in the placebo arms.

The present study has also shown that the PCA3 assay maintains its predictive power for biopsy-detectable PCa in men treated with dutasteride. The sensitivity and specificity curves between the placebo and dutasteride arms were not significantly divergent at either study point. In the dutasteride arm, the AUC (0.668) for the PCA3 score as a continuous variable at year 2 was consistent with that (0.693) in the placebo arm of the REDUCE trial[9] and with findings by Deras et al[7] and Marks et al[5] (both AUC 0.68) in study populations excluding those receiving 5-ARI treatment. The AUC (0.628) at year 4 for PCA3 was lower; however, the 95% CI overlapped that of the year 2 findings, indicating an insubstantial difference between the 2 follow-up points. The trend toward lower sensitivity observed at year 4 versus year 2 might have resulted from the possibility that any PCa remaining after 2 biopsies and 4 years of treatment were smaller. However, in the absence of direct evidence to support this hypothesis, the results of the present study must be viewed as indicating reduced sensitivity at year 4.

Although the serum PSA level is still used to monitor men taking 5-ARIs for benign prostatic hyperplasia, the cutoff for a positive result is considerably decreased and depends on the length of time the patient has been receiving treatment. In the present study, no adjustment to the PCA3 score cutoff values was necessary to yield equivalent clinical performance between the dutasteride and placebo arms.

Importantly, when evaluated using multivariate regression analysis at either year 2 or year 4, the PCA3 score was not attenuated by traditional risk variables, including serum PSA level, age, family history of PCa, or prostate volume. When removing the PCA3 score from the multivariate model at year 2, the predictive power of the remaining variables was significantly diminished compared with the full model, confirming the contribution of the PCA3 score. The PCA3 score does not provide identical information to the PSA level. Rather, the 2 variables provide complementary information at year 2. At year 4, the PCA3 score was informative and the PSA level was not informative for predicting the biopsy outcome.

An additional question addressed in the present study was the performance of the PCA3 score in subjects with high-grade PCa in the dutasteride arm. This is a point of some controversy because conflicting views exist regarding the potential of 5-ARIs to induce high-grade PCa as an adverse effect of the chemoprevention regimen.[19-21] If the PCA3 score demonstrated capability for the early detection of such PCa cases, such fears might be allayed. Although the PCA3 scores were predictive of high-grade PCa at both years 2 and 4, the limited number of such cases (33 and 18 at years 2 and 4, respectively) in our study indicates that the results should be viewed as preliminary only. A specific study powered for the detection of high-grade PCa is required to characterize the performance with statistical confidence.

Additionally, an important limitation of the present study was the lack of availability of pretreatment urine specimens. Therefore, although the median PCA3 scores and clinical performance at a predetermined cutoff were equivalent for the dutasteride and placebo arms, the effect of dutasteride on the PCA3 score for individual patients could not be assessed.

CONCLUSIONS

For the first time in a worldwide study, we considered the utility of the PCA3 assay for predicting PCa in men

receiving dutasteride. The PCA3 assay retained its performance characteristics in this population of men entering the study with 1 previous negative biopsy and an elevated serum PSA level. No adjustment to the PCA3 score cutoff values was necessary to yield equivalent clinical performance between the dutasteride and placebo arms. In addition, the PCA3 scores can increase the diagnostic accuracy when used with the serum PSA level and other clinical information. The results of the present study are particularly important, because dutasteride is widely used to treat lower urinary tract symptoms in men and also because of the developing role of dutasteride as a potential chemopreventive agent.

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APPENDIX

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.urology.2011.03.033.