Detection of High-Grade Prostate Cancer among PLCO Participants Using a Prespecified Four Kallikrein Marker Panel

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Abstract

Purpose—To assess the performance of a four-kallikrein panel, with and without microseminoprotein-beta (MSP), to predict high-grade (Gleason 7+, Gleason Grade Group 2+) prostate cancer (PCa) on biopsy in a multiethnic cohort from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial.

Materials and Methods—Levels of free, intact, total prostate-specific antigen (PSA), human kallikrein-2, and MSP were measured blinded to outcome in cryo-preserved serum from men in the intervention arm of PLCO. Marker levels from 946 men, of whom 100 were African-American, were incorporated into a prespecified statistical model to predict high-grade PCa on biopsy.

Results—The detection of high-grade PCa (n=94, 10%) was enhanced by the four-kallikrein panel with an AUC of 0.79 compared to 0.73 for the Prostate Cancer Prevention Trial (PCPT) risk calculator (increase of 0.060; 95% C.I. 0.032, 0.088; p<0.01). Additionally, the AUC increased from 0.79 to 0.81 when MSP was added to the four-kallikrein panel. In African-American men, the four-kallikrein panel model also enhanced high-grade PCa detection over PSA (AUC 0.80 versus 0.67). As an illustration of clinical implications, use of one cut-point for biopsy (6% risk of

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high-grade PCa) with the four-kallikrein panel model would have eliminated unnecessary biopsies in 42% (397/946) of our cohort while detecting 88% (83/94) of highgrade PCa.

Conclusions—In a multiethnic United States population, the four-kallikrein panel demonstrates improved risk discrimination for high-grade PCa over conventional clinical variables (age, PSA, digital rectal examination) as well as the PCPT risk calculator.

Keywords

prostate cancer; screening; prostate-specific antigen; biopsy

INTRODUCTION

Over the last 20 years, prostate-specific antigen (PSA) has been employed as a screening tool for prostate cancer (PCa). Although PSA provides a significant benefit over digital rectal examination (DRE) alone and is associated with clinically significant PCa,[1] a moderately elevated PSA has poor specificity and positive predictive value. For instance, the rate of positive biopsy was 24% in the European Randomized Study of Prostate Cancer Screening (ERSPCS) and 35% in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial.[2,3] Furthermore, of those men with positive biopsy, less than a third have clinically aggressive disease that requires consideration for curative intervention.[4]

A series of retrospective cohort studies have investigated a multivariable model that combines four kallikrein marker levels in blood — total PSA, free PSA, intact PSA, and human kallikrein-related peptidase 2 (hK2)—with clinical characteristics (age, DRE and history of prior negative biopsy). The fourkallikrein (4K) panel demonstrated improved risk discrimination compared to PSA and clinical characteristics alone. Decision analyses have demonstrated that use of the panel would reduce the number of biopsies performed, while missing few cases of high-grade.[5–9] The accuracy of the 4K panel to predict aggressive disease on radical prostatectomy has also been demonstrated.[10]

Although studied and validated in European populations,[5–10] the 4K panel has not been extensively evaluated in United States men.[11] More importantly, as the European population was almost exclusively Caucasian, the performance characteristics of the 4K panel need to be studied in African-Americans, who more often present with advanced and aggressive disease, and are more likely to die from PCa.[12,13] We examine a prespecified prediction model using the 4K panel to diagnose high-grade PCa, using preserved serum samples of men from the PLCO screening trial, who had a biopsy for elevated PSA (4.0 ng/mL). As a secondary aim, we examine the benefit of another candidate blood biomarker, microseminoprotein-beta (MSP),[14] in combination with the 4K panel.

MATERIALS AND METHODS

Study cohort

With institutional review board approval from all study centers, we received pre-biopsy patient serum samples from the PLCO bio-repository and assayed the levels of the four kallikrein markers (free PSA, intact PSA, total PSA, and hK2) as well as MSP. The 4K panel

was combined with various clinical parameters in a prespecified statistical model. Biopsy results were released to the study statisticians only after predictions were submitted to a third party. Accordingly, assays, modeling and outcome were assessed independently and blindly.

Our study cohort included patients from the intervention arm of PLCO, who provided consent, had no prior history of cancer, had no biopsies prior to randomization, were aged <75 years, had PSA 4 ng/mL during the biopsy year, documented Gleason score on biopsy, and has serum from the biopsy year available in the bio-repository. In PLCO, a positive screening result (suspicious DRE or PSA 4 ng/mL) in the intervention arm resulted in a notification to the patients' primary care physician, who determined the subsequent diagnostic evaluation.[3] The biopsy Gleason score was obtained by PLCO trial staff and collected by medical data abstractors. No central pathologic review was performed. All samples from eligible African-American, non-Hispanic men were included (n=113), and 887 samples were selected randomly from the remaining eligible men to build our study cohort (n=1000). Patients with missing data were excluded from further analysis (n=54), leaving a final sample of 946, 100 of whom were non-Hispanic African-Americans.

Laboratory methods

Immunoassay measurements of total and free PSA,[15] intact PSA,[16] hK2,[17] and MSP,[18] were conducted on AutoDelfia® 1235 automatic immunoassay systems (Wallenberg Research Laboratories, Department of Translational Medicine, Lund University, Skåne University Hospital, Malmö, Sweden). Free and total PSA were measured using the dual-label DELFIA Prostatus® total/free PSA-Assay (Perkin-Elmer, Turku, Finland) calibrated against the World Health Organization (WHO) 96/670 (PSA-WHO) and WHO 68/668 (free PSA-WHO) standards. The measurements of intact PSA and hK2 were performed with F(ab')2 fragments of the monoclonal capture antibodies as previously reported.[19] The intact PSA assay measures only single-chain intact forms of free PSA as the monoclonal 4D4 IgG used in this assay does not bind multi-chain forms of free PSA cleaved at Lys_{145} or Lys_{146}. Production and purification of the polyclonal rabbit anti-MSP antibody, protocols for biotinylation and Europium labeling of the anti-MSP antibody, and performance of the MSP-immunoassay were performed as previously reported.[14] All assay measurements were conducted blinded to biopsy result.

Predictive Models

We assessed the accuracy of models to predict prostate biopsy outcome among men in our study cohort. Primarily we were interested in the accuracy of a model utilizing age, the 4K panel, and DRE to predict high-grade cancer on biopsy. Gleason score 7 or Gleason Grade Group[20] (GGG) 2 were considered to be high-grade PCa. In order to assess the added clinical utility of the 4K panel, we compared these results to a model based on age, total PSA, and DRE, as well as the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC).[21] Additional predictive models that included various combinations of the clinical variables (age, PSA, DRE, 4K panel), as well as MSP, were examined. All models, other than those testing the value of incorporating MSP, were prespecified. The 4K and PSA models were derived from the Rotterdam section of the ERSPCS.[6]

Statistical Methods

The discrimination of the predictive models was assessed using receiver operating characteristic (ROC) curves and calculations of the area under the curve (AUC). The calibration of the models was also assessed visually by plotting the predicted risk against the observed risk of PCa. A perfectly calibrated model would have predicted risk and observed risk fall along a 45 degree line, indicating the risk obtained from the model reflects the actual observed risk of PCa on biopsy. Decision curve analysis was used to assess the clinical impact of the models.[22] Due to the study sampling scheme, with intended over-sampling of African-American patients, all cohort-level statistics (e.g. AUC, calibration, decision curve analysis, and clinical consequences) have been weighted to represent the original PLCO cohort. Differences in discrimination were calculated and confidence intervals for the difference were estimated using clustered bootstrap re-sampling.

The analyses were then repeated separately for African-American men and for men of other races to assess differences in the performance of the model by race. As differences in prostate biopsy outcomes were observed between African-American men and men of other races, the models were refit to include race as a covariate. Constrained logistic regression was utilized to assess the magnitude of the adjustment to the risk prediction required for African-American men. Race and the risk prediction were entered into the regression model. Model risk was entered on the inverse-logit scale and the coefficient was constrained to be one.

Logistic regression was also utilized to assess whether MSP improves the performance of the models including the kallikrein makers. Ten-fold cross validation was utilized when assessing the performance of the model including MSP to account for the fact that models were built and evaluated on the same data set. All analyses were conducted using Stata 13.0 (Stata Corporation, College Station, Texas).

RESULTS

Characteristics of the study sample are shown in Table 1 and Supplementary Table 1; 24% (230/946) of patients had low-grade (Gleason 6, GGG 1) PCa and 10% (94/946) of patients had high-grade (Gleason 7, GGG 2) PCa. African-Americans constituted 11% (100/946) of the final cohort compared to 7% (113/1864) of the PLCO intervention arm.

Discrimination of the prespecified statistical models are shown in Table 2. The 4K panel significantly improved the AUC for predicting high-grade PCa compared to the base model of PSA, age and DRE (increase in AUC of 0.080; 95% C.I. 0.059, 0.105; p<0.01) and compared to the PCPT risk calculator (increase of 0.060; 95% C.I. 0.032, 0.088; p<0.01). When stratifying the cohort by race, the 4K panel discrimination for high-grade PCa was higher for African-Americans (AUC 0.80) than for men of other races (AUC 0.78); however, the confidence intervals for the differences in AUC by race were not statistically significant (95% C.I. –0.10, 0.13).

The calibration plot for the 4K model with and without DRE is provided in Figure 1. The calibration plot demonstrated good agreement for patients with estimated risk of high grade PCa of 20% of less.

The decision curve analysis for the 4K model with and without MSP is provided in Figure 2. The decision curve analysis demonstrates improved clinical outcomes over biopsy all or no biopsy across the range of reasonable threshold probabilities for high-grade PCa. The clinical performance of using these models at various risk thresholds to perform biopsy as compared to PSA alone is provided in Table 3. At one illustrative threshold, 6% risk of high-grade disease, use of the panel in 1000 men would reduce the number of biopsies by 420 and the number of low-grade PCa diagnoses by 63. Of the 420 men avoiding biopsy, 11 (2.6%) would harbor high-grade disease. The clinical outcomes of using the 4K model to perform biopsy across a range of thresholds is illustrated separately in Figure 3.

African-American race was significantly associated with high-grade PCa (OR 2.83; 95% C.I. 1.38, 5.81) after adjusting for the 4K model score. Inclusion of race with the 4K model improved discrimination for high-grade PCa (AUC 0.80 versus 0.79).

Adjusting for the 4K panel result, MSP was a significant predictor of high-grade PCa (OR 0.96, 95% C.I. 0.94, 0.98; p<0.01). The addition of MSP to the 4K panel provided improvement in risk discrimination (0.81, 95% C.I. 0.77, 0.84 versus 0.79, 95% C.I. 0.75, 0.82). The 4K panel with MSP model demonstrated an increased net benefit over the 4K panel alone at all threshold probabilities in the decision curve analysis (Figure 2).

DISCUSSION

In our study of the 4K panel in participants from the intervention arm of PLCO, we found that a prespecified 4K panel model improved predictive discrimination for high-grade PCa compared to other clinical risk determinants (age, PSA, DRE, and the PCPTRC). Calibration was generally good, and decision curve analysis demonstrated that the 4K panel would improve clinical outcomes as compared to biopsy in all men. As such, use of the 4K panel to determine biopsy indication would importantly reduce the number of biopsies performed, while missing few high-grade PCa.

As our study cohort was generated from the PLCO trial, the study results are constrained to the inclusion and exclusion criteria of the original trial. Specifically, the improved risk discrimination demonstrated with the use of the 4K panel model cannot necessarily be applied to men aged greater than 74 years, with PSA less than 4 ng/mL, or who have undergone a prior biopsy. Given the questionable benefit of PCa screening, diagnosis, or treatment in older men,[23] the most clinically relevant limitation listed above is the inability to apply our study results to men with prior biopsy. In these men, particularly those with prior negative biopsies, adjuvant diagnostic tests (such as magnetic resonance imaging) may be necessary to improve risk stratification and reduce unnecessary subsequent biopsies.

The 4K panel provided a slightly greater improvement in risk discrimination for African-Americans (AUC 0.803) as compared to other races (AUC 0.781). In common with other studies, African-American race was found to be a significant predictor for high-grade PCa,

independent of the 4K panel. Although we were unable to demonstrate that the 4K panel is significantly superior in African-Americans compared to other races, an analysis for which we had limited power, our finding suggests that improvements afforded by the 4K panel are highly unlikely to be worse in this racial group.

MSP was found to improve discrimination when added to the 4K panel. Decision analysis illustrates a small improvement in clinical outcome by using MSP with the 4K panel compared to the 4K panel alone. An extension of this concept has been demonstrated in the Stockholm 3 study; in a prospective fashion, Gronberg et al. used a combination of serum biomarkers (of which 5/6 are the same as the ones used in the current study but measured on a different instrument platform), single nucleotide polymorphisms, and traditional clinical characteristics to refine high grade PCa detection.[24]

The risk discrimination found in our study was similar to that of a prospective study of a commercialized 4K based model ("4Kscore") applied to United States men accrued in routine urologic practice (AUC 0.82, 95%CI 0.79 to 0.85).[25] The improvement in risk discrimination for high-grade PCa over commonly used clinical tools (e.g. PSA, PCPTRC) was also similar in both studies. There is also similarity in findings with respect to race, with both studies finding that the discrimination of the 4K panel was higher in African-American men compared to other races, although the limited number of African-Americans in both studies prevent a definitive conclusion. The key result in each case is that the 4K model significantly improves high-grade PCa risk discrimination in a multi-ethnic United States population, confirming the initial European results, despite differences in racial composition.

Given the current controversy with PCa screening and associated overdiagnosis and overtreatment,[23] the need for clinical tools to provide improved risk stratification prior to prostate biopsy, particularly for high-grade PCa,[26] is critical to improving PCa care in the United States. The results of this study confirm that the 4K panel can be utilized as such a tool to reduce the number of biopsies performed while minimizing the high-grade PCa that would be delayed or missed. Reduction in prostate biopsies performed, and thus reduction in the diagnosis of low-grade PCa, with minimal sacrifices in the detection of high-grade PCa, would likely provide a net positive impact on both total healthcare costs as well as patient morbidity.[27,28] Future studies must consider the costs associated with the use of each additional biomarker (e.g. MSP), the comparative effectiveness of magnetic resonance imaging as a risk stratification tool over biomarkers,[29] and the optimal cost-effective strategy for timing these tests prior to biopsy.

This study is not without limitations. As discussed above, the study results may not clearly be applied to men aged greater than 74 years, with PSA less than 4 ng/mL, or who have undergone prior biopsy. Although our study cohort was built to oversample African-American participants in PLCO and approached the most recent United States racial demographics (12.6% the U.S. population on the most recent census identified as African-American),[30] the study was likely underpowered to detect a significant difference in the risk discrimination with the 4K panel in African-Americans over other races. The overall incidence of high-grade PCa in our study was lower than in some contemporary studies, and as a result the 4K panel overestimated high-grade PCa risk at higher clinical risk thresholds

(greater than 20%, Figure 1). This is likely less clinically meaningful as those with substantially high clinical risk do not represent the majority of the screened population, and furthermore, these patients would be recommended for biopsy whether their risk of high-grade PCa was 40% based on PSA or 60% with the 4K panel model.

CONCLUSIONS

The use of the 4K panel in a selected population of PLCO participants confirms the results of prior studies, that the 4K panel can improve detection of high-grade PCa in a multi-ethnic United States cohort. Furthermore, the improvement in risk discrimination is similar among African-American men. Finally, the addition of a fifth serum biomarker, MSP, provides an incremental improvement in the ability to identify patients with high-grade PCa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

PSA	prostate-specific antigen
PCa	prostate cancer
DRE	digital rectal examination
ERSPC	European Randomized Study of Prostate Cancer Screening
PLCO	Prostate, Lung, Colorectal, Ovarian
hK2	human kallikrein-related peptidase 2
4K	four-kallikrein
MSP	microseminoprotein-beta
WHO	World Health Organization
GGG	Gleason Grade Group
PCPTRC	Prostate Cancer Prevention Trial Risk Calculator
ROC	receiver operating characteristic
AUC	area under the curve

Age + Four-Kallikrein Panel   Age + Four-Kallikrein Panel + DRE
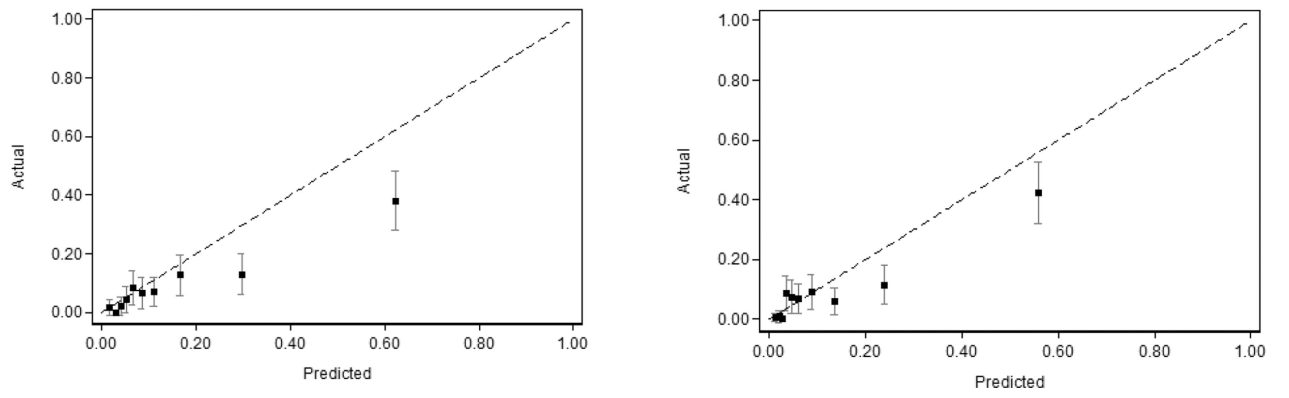
Figure 1.
Calibration plot of the four-kallikrein model predicting high-grade prostate cancer.

Age + Four-Kallikrein Panel (black dashed line)
Age + Four-Kallikrein Panel + DRE (grey dashed line)
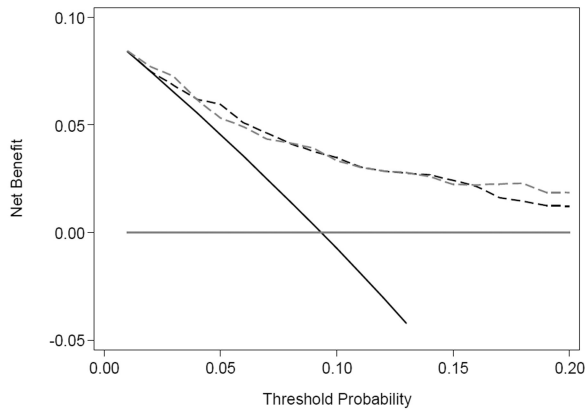
Age + Four-Kallikrein Panel (black dashed line)
Age + Four-Kallikrein Panel + MSP (grey dashed line)
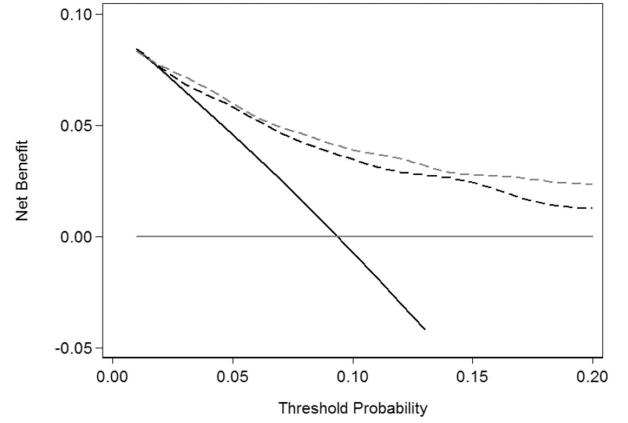
Figure 2.
Decision curve analysis of the four-kallikrein model predicting high-grade prostate cancer.
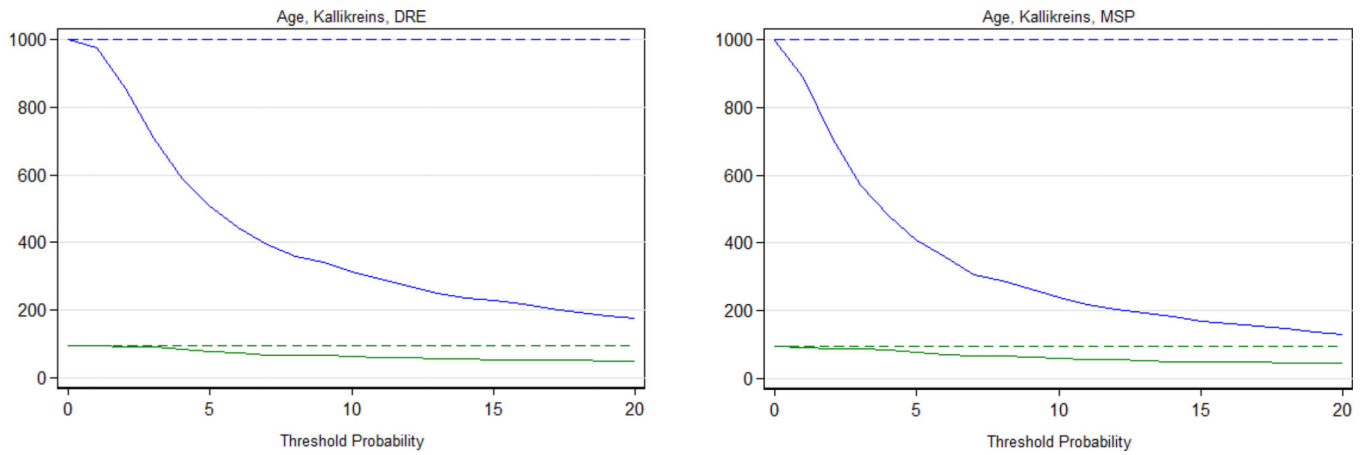
Figure 3.
Clinical consequences of using age, the four-kallikrein panel and DRE (left panel) and the four-kallikrein panel where DRE was replaced with MSP (right panel) to identify men for biopsy at varying biopsy thresholds. Results presented per 1000 men. The blue solid lines represent the number of men requiring prostate biopsy utilizing the respective models, dashed blue line marks the biopsy all men alternative. The solid green lines represent the number of high-grade cancers found, dashed green line marks the number of high-grade cancers found if all men are biopsied.

Table 1

Characteristics of selected patients with complete data. Statistics presented are median (IQR) or frequency (percent).

	Overall N=946	No Cancer (N=622; 66%)	Low-Grade Cancer** (N=230; 24%)	High-Grade Cancer*** (N=94; 10%)	Other Races (N=846; 89%)	Black, Non-Hispanic (N=100; 11%)
Age, years	64 (60, 68)	64 (60, 68)	65 (61, 69)	66 (61, 69)	64 (60, 68)	64 (60, 69)
Abnormal DRE	141 (15%)	67 (11%)	45 (20%)	29 (31%)	123 (15%)	18 (18%)
Race						
White, non-Hispanic	796 (84%)	549 (88%)	179 (78%)	68 (72%)	796 (94%)	0 (0%)
Black, Non-Hispanic	100 (11%)	41 (6.6%)	37 (16%)	22 (23%)	0 (0%)	100 (100%)
Hispanic	22 (2.3%)	11 (1.8%)	9 (3.9%)	2 (2.1%)	22 (2.6%)	0 (0%)
Asian	20 (2.1%)	16 (2.6%)	3 (1.3%)	1 (1.1%)	20 (2.4%)	0 (0%)
Pacific Islander	4 (0.4%)	3 (0.5%)	1 (0.4%)	0 (0%)	4 (0.5%)	0 (0%)
American Indian	2 (0.2%)	1 (0.2%)	1 (0.4%)	0 (0%)	2 (0.2%)	0 (0%)
Unknown	2 (0.2%)	1 (0.2%)	0 (0%)	1 (1.1%)	2 (0.2%)	0 (0%)
Family History of PCa	102 (11%)	61 (10%)	23 (10%)	18 (19%)	93 (11%)	9 (9.0%)
Unknown	8 (0.8%)	3 (0.5%)	3 (1.3%)	2 (2.1%)	7 (0.8%)	1 (1.0%)
Total PSA, ng/mL	5.8 (4.8, 7.6)	5.6 (4.8, 7.0)	6.0 (4.8, 8.2)	8.0 (5.3, 17.4)	5.8 (4.8, 7.5)	5.9 (5.0, 8.5)
Free PSA, ng/mL	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)	1.0 (0.7, 1.4)	1.1 (0.7, 1.8)	1.1 (0.8, 1.6)	1.0 (0.8, 1.4)
Intact PSA, ng/mL	0.72 (0.54, 1.01)	0.74 (0.57, 1.00)	0.67 (0.49, 0.93)	0.75 (0.50, 1.24)	0.73 (0.55, 1.01)	0.68 (0.50, 0.93)
hK2, ng/mL	0.08 (0.05, 0.12)	0.07 (0.05, 0.11)	0.08 (0.05, 0.12)	0.10 (0.06, 0.18)	0.08 (0.05, 0.12)	0.06 (0.04, 0.09)
MSP, ng/mL (N=938)	21 (14, 30)	23 (15, 32)	18 (13, 27)	16 (11, 25)	22 (15, 31)	15 (11, 22)
Risk of Cancer on Biopsy (%)						
Age + PSA	24 (22, 28)	24 (22, 27)	25 (22, 30)	30 (23, 54)	24 (22, 28)	24 (22, 30)
Age + PSA + DRE	19 (17, 26)	19 (17, 22)	21 (17, 39)	31 (19, 51)	19 (17, 25)	20 (17, 35)
Age + Kallikrein Markers	38 (30, 51)	35 (26, 44)	45 (37, 64)	61 (44, 90)	38 (30, 51)	42 (32, 55)
Age + Kallikrein Markers + DRE	35 (27, 50)	31 (24, 41)	42 (32, 64)	62 (39, 89)	34 (27, 50)	38 (30, 55)
*PCPT risk calculator estimate	30 (26, 35)	29 (26, 33)	32 (26, 39)	38 (31, 49)	29 (26, 33)	40 (36, 48)
Risk of Gleason 7 Cancer on Biopsy (%)						
Age + PSA	8 (6, 10)	7 (6, 9)	8 (6, 12)	10 (7, 24)	8 (6, 10)	8 (6, 12)
Age + PSA + DRE	5 (4, 7)	4 (3, 6)	5 (4, 12)	8 (4, 23)	5 (3, 7)	5 (4, 10)
Age + Kallikrein Markers	7 (4, 16)	6 (3, 10)	12 (6, 28)	25 (10, 59)	7 (4, 16)	10 (5, 21)

	Overall N=946	No Cancer (N=622; 66%)	Low-Grade Cancer ** (N=230; 24%)	High-Grade Cancer *** (N=94; 10%)	Other Races (N=846; 89%)	Black, Non-Hispanic (N=100; 11%)
Age + Kallikrein Markers + DRE	5 (3, 13)	4 (2, 8)	10 (4, 23)	25 (7, 54)	5 (3, 13)	8 (3, 16)
PCPT risk calculator estimate *	9 (7, 14)	8 (7, 12)	11 (7, 18)	15 (10, 25)	9 (7, 12)	20 (17, 30)
Biopsy Gleason						
No Cancer	622 (66%)	622 (100%)	0 (0%)	0 (0%)	581 (69%)	41 (41%)
Low-Grade Cancer **	230 (24%)	0 (0%)	230 (100%)	0 (0%)	193 (23%)	37 (37%)
Gleason Score 7 (GGG 2 or 3)	72 (7.6%)	0 (0%)	0 (0%)	72 (77%)	54 (6.4%)	18 (18%)
Gleason Score 8 (GGG 4 or 5)	22 (2.3%)	0 (0%)	0 (0%)	22 (23%)	18 (2.1%)	4 (4.0%)

DRE = digital rectal examination, PCa = prostate cancer, PSA = prostate-specific antigen, hK2 = human kallikrein-2, MSP = microseminoprotein-beta, PCPT = Prostate Cancer Prevention Trial, GGG = Gleason Grade Group

*
PCPT risk calculator estimate = prespecified PCPT risk calculator version 2.0 model

**
Low-grade Cancer includes Gleason score 6 (Gleason Grade Group 1)

***
High-grade Cancer includes Gleason score 7 (Gleason Grade Group 2)

Table 2

Model discrimination for predicting high-grade cancer

a) Overall findings

	AUC	95% CI
Age + PSA	0.691	0.641, 0.735
Age + Four-Kallikrein Panel	0.786	0.748, 0.816
Age + PSA + DRE	0.706	0.660, 0.746
PCPT risk calculator [*]	0.726	0.684, 0.771
Age + Four-Kallikrein Panel + DRE	0.786	0.748, 0.815
Age + Four-Kallikrein Panel + MSP	0.809	0.774, 0.838
Age + Four-Kallikrein Panel + MSP + DRE	0.810	0.775, 0.840

b) Discrimination by race

	African-American	Other Races	Difference	95% CI
Age + PSA	0.671	0.694	−0.023	−0.19, 0.14
Age + Four-Kallikrein Panel	0.803	0.781	0.022	−0.10, 0.13
Age + PSA + DRE	0.691	0.710	−0.019	−0.18, 0.14
Age + Four-Kallikrein Panel + DRE	0.790	0.783	0.007	−0.12, 0.12

[*] PCPT risk calculator estimate = prespecified PCPT risk calculator version 2.0 model

AUC = area under the curve
CI = confidence interval
PSA = prostate-specific antigen
DRE = digital rectal examination
MSP = beta-microseminoprotein

Table 3

Clinical implications of using models to determine biopsy.

Biopsy Threshold (risk of high-grade* cancer)	No. Biopsied	Biopsies Avoided (%)	Cancers Found	Cancers Delayed	High-grade* Cancers Found	High-grade* Cancers Delayed
Biopsy All Men	1000	0 (0%)	330	0	93	0
Age and PSA						
4%	946	54 (5.4%)	310	20	88	5
6%	734	266 (27%)	255	75	79	14
8%	460	540 (54%)	192	139	66	28
10%	285	715 (72%)	144	186	52	42
4K model						
4%	749	251 (25%)	302	28	89	4
6%	580	420 (42%)	256	74	83	11
8%	466	534 (53%)	227	104	75	18
10%	380	620 (62%)	197	133	69	24

PSA = prostate-specific antigen, 4K = four-kallikrein panel

*
High-grade cancer includes Gleason score 7 (Gleason Grade Group 2)