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Prostate Cancer

A Multi-institutional Prospective Trial in the USA Confirms that the 4Kscore Accurately Identifies Men with High-grade Prostate Cancer

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Abstract

Background: The 4Kscore combines measurement of four kallikreins in blood with clinical information as a measure of the probability of significant (Gleason ≥7) prostate cancer (PCa) before prostate biopsy.
Objective: To perform the first prospective evaluation of the 4Kscore in predicting Gleason ≥7 PCa in the USA.
Design, setting, and participants: Prospective enrollment of 1012 men scheduled for prostate biopsy, regardless of prostate-specific antigen level or clinical findings, was conducted at 26 US urology centers between October 2013 and April 2014.
Intervention: The 4Kscore.
Outcome measurements and statistical analysis: The primary outcome was Gleason ≥7 PCa on prostate biopsy. The area under the receiver operating characteristic curve, risk calibration, and decision curve analysis (DCA) were determined, along with comparisons of probability cutoffs for reducing the number of biopsies and their impact on delaying diagnosis.
Results and limitations: Gleason ≥7 PCa was found in 231 (23%) of the 1012 patients. The 4Kscore showed excellent calibration and demonstrated higher discrimination (AUC 0.82) and net benefit compared to a modified Prostate Cancer Prevention Trial

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Risk Calculator 2.0 model and standard of care (biopsy for all men) according to DCA. A possible reduction of 30–58% in the number biopsies was identified with delayed diagnosis in only 1.3–4.7% of Gleason ≥7 PCa cases, depending on the threshold used for biopsy. Pathological assessment was performed according to the standard of care at each site without centralized review.
Conclusion: The 4Kscore showed excellent diagnostic performance in detecting significant PCa. It is a useful tool in selecting men who have significant disease and are most likely to benefit from a prostate biopsy from men with no cancer or indolent cancer.
Patient summary: The 4Kscore provides each patient with an accurate and personalized measure of the risk of Gleason ≥7 cancer to aid in decision-making regarding the need for prostate biopsy.

1. Introduction

Although prostate cancer is the most common cancer among US men [1], screening for prostate cancer using measurement of serum prostate-specific antigen (PSA) has come under much criticism [2]. Results from randomized controlled trials indicate that PSA screening leads to a significant risk of overdiagnosis and overtreatment [3–5]. More than one million men undergo prostate biopsy each year in the USA, with the majority showing either no prostate cancer or low-risk disease that is unlikely to impact quantity or quality of life [6]. Each biopsy represents real harm to the patient in terms of anxiety, bleeding, discomfort, and risk of infection requiring hospitalization [6,7]. Biomarkers that can accurately predict the risk of significant prostate cancer and avoid unnecessary biopsies are critically needed.

A panel of four kallikrein proteins has been evaluated in blood samples from over 7500 prebiopsy patients in multiple European cohorts [8–13]. The four kallikreins studied were total PSA, free PSA, intact PSA, and human kallikrein 2 (hK2). The results demonstrate discrimination between men with pathologically indolent disease and men with aggressive disease.

Quantification of these four kallikreins combined with age, digital rectal examination (DRE) findings, and history of prior prostate biopsy are elements of the test now known as the 4Kscore. Although previous results for the four-kallikrein test were impressive, they were derived from retrospective studies in European cohorts. The four-kallikrein panel has never been assessed in a prospective fashion, nor has it been validated in the USA. We wanted to determine the possible impact of the 4Kscore in contemporary practice in the USA by investigating the 4Kscore for predicting significant (Gleason ≥7) prostate cancer in a multi-institutional prospective study of men referred for prostate biopsy.

2. Patients and methods

2.1. Patient population

This prospective study enrolled consecutive patients referred for prostate biopsy at 26 urology centers across the USA between October 2013 and April 2014. All patients had serum PSA measurement and DRE performed by a urologist. A blood sample for kallikrein measurement was collected in a K_2EDTA blood tube before prostate biopsy for each patient. A minimum of ten needle cores at biopsy was required for inclusion in the study. Exclusion criteria included a previous diagnosis of prostate cancer, DRE within 96 h before phlebotomy, or 5-alpha reductase inhibitor therapy in the previous 6 mo. Men who underwent invasive urological procedures for benign prostatic hyperplasia or a prostate biopsy within the previous 6 mo were also excluded. These exclusions were necessary to prevent any potential influence on kallikrein levels. Histopathologic examination of the biopsy specimens was performed according to the established practice at each study site. Demographic and clinical information was collected in a standardized fashion. All patients provided written and informed consent for involvement in the study and collection of data and specimens after institutional review board approval at each site.

2.2. Laboratory methods

All phlebotomy samples were handled and shipped according to the study protocol to the OPKO Laboratory (Nashville, TN, USA) for four-kallikrein testing. The kallikrein measurements were performed without knowledge of the histopathology results. A total and free PSA assay (Roche Diagnostics, Indianapolis, IN, USA) approved by the US Food and Drug Administration was used instead of the Perkin Elmer AutoDELFIA ProStatus PSA free/total assays used in previous European studies of the kallikrein markers [8].

2.3. Evaluation of the 4Kscore

The four-kallikrein algorithm was developed based on data from European Randomized Study of Screening for Prostate Cancer (ERSPC) studies [8–13] and the Prostate Testing for Cancer and Treatment (ProtecT) study, in which 4765 men without a prior negative prostate biopsy and PSA >3 ng/ml underwent a ten-core biopsy [14]. The ProtecT algorithm uses plasma measurement of four kallikreins and includes patient age.

The targeted enrollment for this study was 1300 men. The first 300 patients enrolled in the study entered a calibration phase. Owing to differences between the 4Kscore and the ProtecT algorithm (addition of DRE, prior biopsy status) and differences between the ProtecT cohort and the US study population (use of freshly drawn blood samples and no PSA or age restrictions), data for these 300 patients were used to assess whether any modifications to the 4Kscore algorithm were needed before application to a contemporary population of US men scheduled for prostate biopsy. Calibration of the 4Kscore in these 300 patients revealed that no modification to the algorithm was necessary.

The 4Kscore provides a probability score of 0–100% and reflects the probability that a patient will have significant prostate cancer on biopsy.

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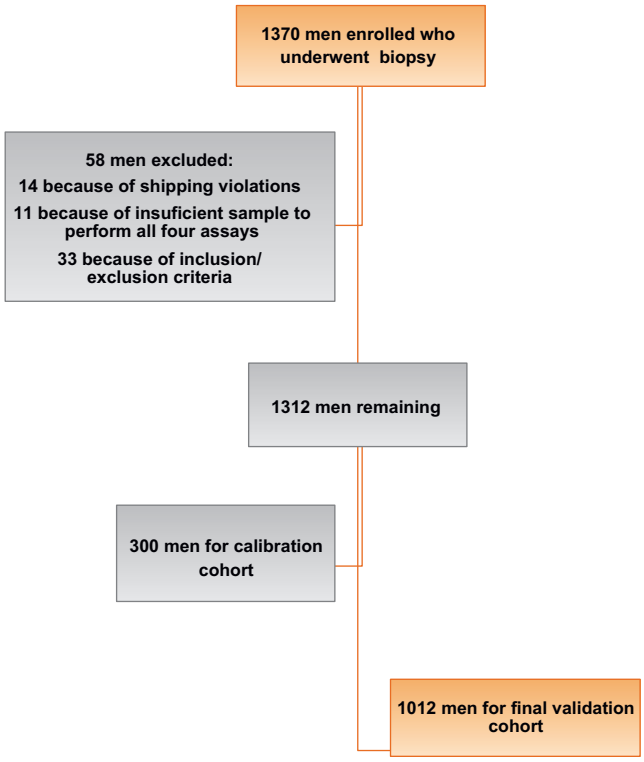

Fig. 1 – Patient flow chart.

Significant prostate cancer was defined as Gleason ≥7 to represent a clinically relevant tumor.

2.4. Statistics

In total, 1370 men were enrolled in the study. Of these, 58 were excluded because of delayed shipping of blood samples and noncompliance with study inclusion and exclusion criteria (Fig. 1), leaving 300 men in the calibration phase and 1012 for validation of the 4Kscore. Demographic and clinical differences between participants with no cancer, Gleason 6 cancer, or Gleason ≥7 cancer were compared using the Kruskal-Wallis test for continuous variables and a chi-square test for categorical variables. The accuracy of the 4Kscore was assessed using the area under the receiver operating characteristic curve (AUC), calibration plots, and decision curve analysis (DCA). AUC assesses how well a model discriminates between patients with and without Gleason ≥7 cancer. The calibration plot illustrates the level of agreement between the 4Kscore predictions and the true risk of Gleason ≥7 cancer. DCA was used to investigate potential clinical effects of the 4Kscore by reporting its net benefit in comparison to that of biopsy-all and biopsy-none strategies [15]. Because biopsy was indicated for all the men in our cohort, the biopsy-all strategy is equivalent to current practice in the USA.

Finally, various 4Kscore cutoffs were explored to determine the number of biopsies that could be avoided and the number of Gleason ≥7 cancers for which diagnosis might be delayed if a threshold probability of Gleason ≥7 cancer was applied as a criterion for prostate biopsy. The accuracy of the 4Kscore was also compared to a modified Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) 2.0, incorporating age, race, DRE, PSA, and prior biopsy to obtain a predicted probability of high-grade prostate cancer [2]. Since information regarding family history, which is included in the PCPTRC 2.0, was not available, we refer to our use of the model as modified. All analyses were specified before the study commenced. Statistical analyses were conducted using Stata 12.0 (Stata Corp., College Station, TX, USA).

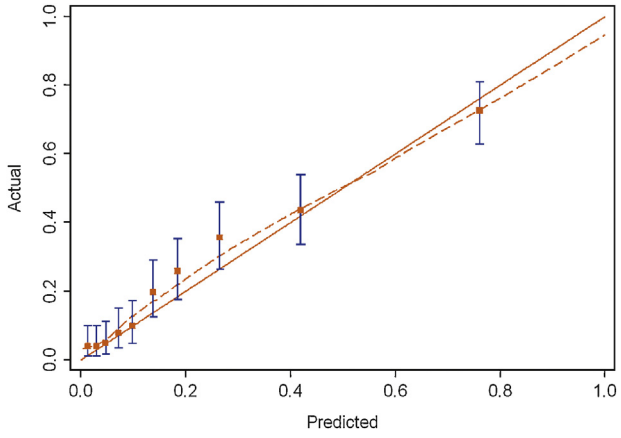

Fig. 2 – Model calibration showing predicted versus actual Gleason ≥7 cancer detected using the 4Kscore in the validation cohort.

3. Results

Patient enrollment for this prospective study is illustrated in Figure 1. There were no significant differences in demographic and clinical characteristics between the calibration and validation cohorts (Supplementary Table 1). Demographic and clinical characteristics by cancer status are shown in Table 1. Among the 1012 men enrolled in the validation phase, 470 (46%) were diagnosed with prostate cancer and 231 (23%) were diagnosed with Gleason ≥7 prostate cancer. Men with prostate cancer tended to be older and had a lower rate of previous biopsy. They also had higher total PSA, lower free/total PSA ratio, and higher intact PSA and hK2 levels compared to men with no cancer. The 4Kscore showed near-perfect calibration, with the predicted probabilities of Gleason ≥7 cancer accurately describing the true risk observed in the cohort (Fig. 2). The predictive accuracy of the 4Kscore was compared to a modified PCPTRC 2.0 and showed superior discrimination in detecting Gleason ≥7 prostate cancer (AUC 0.82 versus 0.74, $p < 0.0001$). A post hoc analysis showed that each kallikrein added significantly to the model discrimination (Table 2). When comparing discrimination using the 4Kscore among African American and Caucasian men, we found that the confidence intervals for the difference in AUC crossed zero (−0.064 to 0.119), suggesting no significant difference in test performance between the two groups.

The 4Kscore showed a higher net benefit compared to modified PCPTRC 2.0 at all threshold probabilities used in common clinical practice according to DCA (Fig. 3). The results also suggest that the 4Kscore improves on the current standard of care (all patients undergoing biopsy).

The number of biopsies that could have been avoided and the proportion of Gleason ≥7 cancers for which diagnosis could have been delayed for various 4Kscore cutoffs were investigated (Table 3). For instance, using a strategy whereby a biopsy would be performed for a ≥9% probability of Gleason ≥7 cancer, 434 (43%) biopsies would

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Table 1 – Patient demographic and clinical variables among the 1012 men in the validation cohort categorized by cancer status

	Negative biopsy	Low-grade PCa	Gleason ≥7 PCa	*p* value
Number	542	239	231	
Age at blood draw (yr)	63 (57–68)	64 (59–69)	66 (61–72)	<0.0001
<50 yr	30 (5.5)	6 (2.5)	3 (1.3)	
50–75 yr	481 (89)	220 (92)	197 (85)	
>75 yr	31 (5.7)	13 (5.4)	31 (13)	
Race				
African American	44 (8.1)	14 (5.9)	27 (12)	0.014
Caucasian	458 (85)	218 (91)	193 (84)	
Hispanic	28 (5.2)	4 (1.7)	4 (1.7)	
Other	10 (1.8)	3 (1.3)	4 (1.7)	
Unknown	2 (0.4)	0 (0)	3 (1.3)	
Abnormal DRE	127 (23)	50 (21)	70 (30)	0.045
Prior prostate biopsy	139 (26)	38 (16)	22 (10)	<0.0001
Total PSA (ng/ml)	4.38 (2.88–6.25)	4.62 (3.60–6.12)	6.07 (4.37–9.66)	<0.0001
<4 ng/ml	232 (43)	79 (33)	37 (16)	<0.0001
4–10 ng/ml	274 (51)	146 (61)	140 (61)	
10–25 ng/ml	36 (6.6)	11 (4.6)	39 (17)	
>25 ng/ml	0 (0)	3 (1.3)	15 (6.5)	
Free PSA (ng/ml)	0.77 (0.51–1.20)	0.80 (0.54–1.15)	0.81 (0.61–1.27)	0.038
Free/total PSA ratio	21 (15–26)	17 (13–25)	13 (10–19)	<0.0001
Intact PSA (pg/ml)	416 (268–636)	469 (311–654)	511 (360–783)	<0.0001
hK2 (pg/ml)	69 (42–107)	81 (55–120)	107 (63–176)	<0.0001
4Kscore	7 (3–15)	14 (6–25)	34 (17–66)	<0.0001
<5%	206 (38)	44 (18)	12 (5.2)	<0.0001
5–10%	130 (24)	57 (24)	13 (5.6)	
10–15%	77 (14)	29 (12)	23 (10)	
15–20%	46 (8.5)	27 (11)	22 (10)	
>20%	83 (15)	82 (34)	161 (70)	
Clinical stage				
T1A/B		2 (0.8)	1 (0.4)	
T1C		177 (74)	135 (58)	
T2A		40 (17)	36 (16)	
T2B		14 (5.9)	23 (10)	
T2C		6 (2.5)	31 (13)	
T3A		0 (0)	3 (1.3)	
T4		0 (0)	1 (0.4)	
TX		0 (0)	1 (0.4)	
Biopsy Gleason grade				
6		239 (100)	0 (0)	
3 + 4		0 (0)	108 (47)	
4 + 3		0 (0)	59 (26)	
8		0 (0)	35 (15)	
9		0 (0)	26 (11)	
10		0 (0)	3 (1.3)	

PCa = prostate cancer; DRE = digital rectal examination; PSA = prostate-specific antigen; hK2 = human kallikrein 2.
Continuous data are presented as median (interquartile range) and categorical data as *n* (%).

be avoided and diagnosis of only 24 (2.4%) Gleason ≥7 cancers would be delayed. Among these delayed cases, the majority of men (*n* = 15) would have Gleason 3 + 4 disease, and only two (0.2%) men would have Gleason 4 + 4 disease.

Table 2 – Discrimination of Gleason ≥7 cancer using the full 4Kscore and a model without each individual kallikrein

	AUC (95% CI)	Difference	*p* value
Full model	0.821 (0.790, 0.852)		
Model without total PSA	0.655 (0.616, 0.694)	0.167	<0.0001
Model without free PSA	0.699 (0.664, 0.735)	0.122	<0.0001
Model without intact PSA	0.794 (0.760, 0.828)	0.027	0.001
Model without hK2	0.806 (0.774, 0.839)	0.015	0.020
Model without intact PSA and hK2	0.751 (0.714, 0.789)	0.070	<0.0001

AUC = area under the receiver operating characteristic curve; CI = confidence interval; PSA = prostate-specific antigen; hK2 = human kallikrein 2.

4. Discussion

This prospective study involved 26 geographically diverse US urology sites and is the first validation of the four-kallikrein panel outside Europe. The 4Kscore showed excellent discrimination and calibration in identifying patients most likely to benefit from biopsy because of a high risk of having a clinically significant tumor that would require treatment. Accordingly, the test could allow a significant reduction in the number of biopsies performed, while delaying diagnosis for relatively few Gleason ≥7 cancers.

Since its widespread adoption in the 1990s, PSA screening has met with much controversy [2]. It is clear that PSA by itself has several limitations as a biomarker for prostate cancer detection. Most contemporary guidelines have encouraged the consideration of multiple clinical

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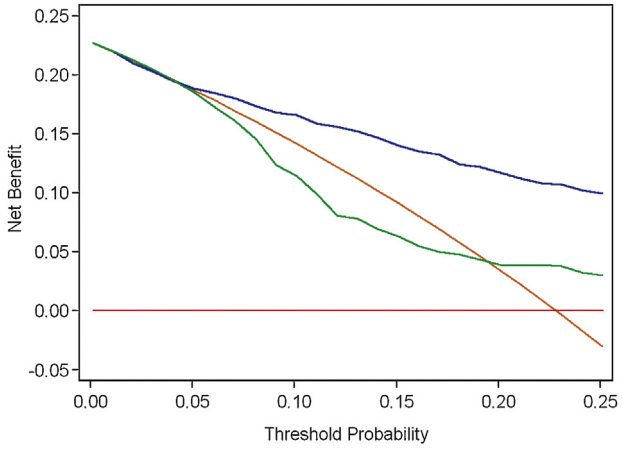

Fig. 3 – Decision curve analysis comparing the 4Kscore to a modified Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) 2.0. Strategies: red line, biopsy no patients; orange line, biopsy all men; green line, PCPTRC 2.0 as criterion for biopsy; and blue line, 4Kscore as criterion for biopsy. The line with the highest net benefit at any particular threshold probability for biopsy will result in the best clinical results.

factors when deciding on the need for prostate biopsy [17]. The PCPTRC 2.0 incorporates age, race, DRE, PSA, family history, and prior biopsy to provide a predicted probability of Gleason ≥7 prostate cancer [16]. Although it is a widely accepted predictive tool that is easy to use, DCA showed that the 4Kscore was more helpful than a modified PCPTRC 2.0 (without family history) in weighing the risks of undergoing an unnecessary biopsy against delaying detection of a significant cancer. By combining important clinical and molecular information, the 4Kscore improves shared decision-making regarding prostate biopsy.

The study adds to a continuum of work that has validated the four kallikrein markers used in this test among multiple European cohorts who participated in the ERSPC. Separate studies for unscreened cohorts included 262 men in France, 740 men in Göteborg, and 2914 men in Rotterdam, revealing an AUC for significant prostate cancer discrimination of 0.84–0.90 [8,9,12]. Similarly, among screened populations of 1241 men in Göteborg and 1501 men in Rotterdam, the AUC obtained for significant prostate cancer discrimination was 0.83 and 0.80, respectively [10,11]. Among 925 men from Rotterdam with a previous negative biopsy, the AUC for significant prostate cancer detection was 0.87 [13]. In all of these cohorts, the proportion of biopsies that could have been avoided ranged from 36% to 82%, while the likelihood of potential delayed diagnosis of significant prostate cancer was minimal (<5%). The current study expanded on these prior studies and validated the four kallikrein markers used in the 4Kscore in a US population, demonstrating equally impressive accuracy for detection of clinically significant prostate cancer.

The 4Kscore is unique in that it provides an individualized prediction of clinically relevant prostate cancer for each patient. Similar to the positive predictive value (PPV), which indicates the risk of having a disease given a positive screening test, the 4Kscore result itself is the personalized risk, or actual probability, of having Gleason ≥7 cancer on prostate biopsy. Alternatively, 100% minus the 4Kscore result is the personalized negative predictive value or probability that a patient will not have Gleason ≥7 cancer on prostate biopsy. This information is beneficial for informed and shared decision-making to meet the goals and expectations of each patient in deciding on the need for prostate biopsy. For instance, an older man with more comorbidities may value a probability cutoff of 15%, allowing a small, but defined risk of delaying diagnosis of a significant cancer if a biopsy is not performed. By contrast, in a younger, healthier, and more risk-averse man, a more conservative cutoff of 6% might more appropriate. Clinical tools that can provide information on the benefits and risks of undergoing prostate biopsy on such a personalized level are critically needed in this era of informed decision-making. Given the increasing focus on screening for high-risk disease [18], a test that could potentially reduce the number of biopsies performed while delaying a minor amount of significant cancers may help many men to avoid the harms of biopsy and the burden of overdiagnosis. Furthermore, the financial benefit of greatly reducing the number of biopsies and the potential complications they may cause has been estimated as an annual saving of $1 billion to the US health care system [19].

It should be acknowledged that no standard criteria were applied in referring men for prostate biopsy. However, omission of such criteria means that the findings are more generalizable to most men currently referred for prostate biopsy in the USA. Furthermore, histopathologic examination was performed at each site according to the established practice, without a centralized pathology assessment. Again, although this may leave more room for variation in histopathologic interpretation, it means that the study is better generalized to most office practices in the USA, where

Table 3 – Biopsies avoided and Gleason ≥7 cancers with delayed diagnosis for various 4Kscore cutoff values

4Kscore cutoff	Biopsies performed (*n*)	Biopsies avoided, *n* (%)	Gleason ≥7 cancers, *n* (%)		Gleason score for delayed diagnosis of Gleason ≥7 cancers, *n* (%)		
			Detected	Delayed diagnosis	3 + 4	4 + 3	4 + 4 or higher
0%	1012	0 (0)	231 (23)	0 (0)	0 (0)	0 (0)	0 (0)
≥6%	705	307 (30)	218 (22)	13 (1.3)	10 (1.0)	3 (0.3)	0 (0)
≥9%	578	434 (43)	207 (20)	24 (2.4)	15 (1.5)	7 (0.7)	2 (0.2)
≥12%	499	523 (51)	199 (20)	32 (3.2)	20 (2.0)	7 (0.7)	5 (0.5)
≥15%	421	591 (58)	183 (18)	48 (4.7)	33 (3.3)	9 (0.9)	6 (0.6)

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expert genitourinary pathologists may not be the standard of care. Complete data for all of the variables included in the PCPTRC 2.0 were not available owing to missing family history status. Although family history is a predictor of any cancer in the PCPTRC 2.0, it is not a predictor of Gleason ≥7 cancer [16]. Therefore, we do not feel that predictions of Gleason ≥7 cancer would significantly differ between a modified PCPTRC 2.0 without family history and the full model. Finally, although we saw no significant difference in discrimination of Gleason ≥7 disease between African Americans and Caucasians, we acknowledge that only 85 African American men were enrolled in the validation cohort and our AUC confidence intervals were wide, which limited our ability to exclude a meaningful difference between the groups. The study had a number of strengths that should be highlighted. This clinical study is the first prospective validation of the kallikrein panel used in the 4Kscore. Moreover, it is the first validation of the test in a cohort of men from multiple sites across the USA. Another strength of the study was the focus on clinically significant (Gleason ≥7) cancer. Combined, these strengths highlight the suitability of the 4Kscore for real-time contemporary practice in the USA.

5. Conclusions

The 4Kscore is a clinical decision aid that combines measurement of blood-based biomarkers with important clinical information. In its first prospective evaluation in the USA, the 4Kscore displayed excellent ability to discriminate between men who are likely to harbor clinically relevant cancer and those who are likely to harbor indolent tumors or no cancer. The test has significant potential to reduce the number of prostate biopsies performed while delaying the diagnosis of only a small number of significant cancers. Furthermore, the ability to quantify a personalized risk estimate of the presence of Gleason ≥7 prostate cancer allows informed and shared decision-making between a patient and his clinician.

Author contributions: Dipen J. Parekh 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: Zappala.
Acquisition of data: All authors.
Analysis and interpretation of data: Sjoberg, Punnen, Parekh.
Drafting of the manuscript: Punnen, Parekh.
Critical revision of the manuscript for important intellectual content: Parekh, Punnen, Sjoberg.
Statistical analysis: Sjoberg.
Obtaining funding: All authors.
Administrative, technical, or material support: All authors.
Supervision: Parekh, Zappala.
Other (specify): None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.10.021.

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