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Assessment of Long Term Outcomes Associated with Urinary Prostate Cancer Antigen 3 and TMPRSS2:ERG Gene Fusion at Repeat Biopsy

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Abstract

BACKGROUND—The long-term health outcomes associated with the use of urinary prostate cancer antigen 3 (PCA3) and TMPRSS2:ERG (T2:ERG) fusion in men with at least one previous negative biopsy and elevated serum prostate specific antigen (PSA) when making repeat biopsy decisions have not been investigated for clinically localized prostate cancer (PCa).

METHODS—We performed decision analysis using a decision tree for men with elevated PSA. The probability of cancer was estimated using the Prostate Cancer Prevention Trial risk calculator (PCPTRC version 2.0). We compared the use of PSA alone with PCA3 and T2:ERG, each used

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Conflict of Interest: S.A.T. is a co-inventor on a patent issued to the University of Michigan on ETS fusions in prostate cancer. The diagnostic field of use has been licensed to Gen-Probe, Inc., who has sublicensed certain rights to Ventana Medical Systems. S.A.T. is a consultant for, and has received honoraria from, Ventana Medical Systems.

independently, in combination with PSA to trigger a repeat biopsy. When PCA3 and T2:ERG were used, a predefined threshold was used to determine whether to perform a repeat biopsy. Biopsy outcomes were defined as positive biopsy with Gleason Score (GS) of <7, 7, or >7, or negative biopsy. Probabilities and estimates of 10-year overall survival and 15-year cancer-specific survival were derived from previous studies and literature review. Outcomes were defined as age and GS dependent 10-year overall survival and 15-year cancer-specific survival, and percentage of biopsies avoided.

RESULTS—Incorporating PCA3 (biopsy threshold 25) or T2:ERG (biopsy threshold 10) into repeat biopsy decisions would have avoided 55.4% and 64.7% of repeat biopsies for the base case patient, respectively; changes in 10-year survival were only 0.93% and 1.41% percent, respectively. Multi-way sensitivity analysis suggests that our results are robust with respect to model parameters.

CONCLUSIONS—The use of PCA3 testing or T2:ERG for repeat biopsy decisions can reduce the number of biopsies substantially without significantly affecting 10-year survival.

Keywords

Prostate cancer; repeat biopsy; urinary biomarkers; survival; prostate cancer antigen 3; TMPRSS2-ERG

INTRODUCTION

Commonly used diagnostic indicators for the early detection of prostate cancer (PCa) include abnormal digital rectal examination (DRE) and an elevated prostate-specific antigen (PSA). Serum PSA levels above 2.5 to 4 ng/ml and/or suspicious DRE may indicate the presence of PCa; however, the performance of PSA alone with a cutoff of 4 ng/ml is reported to yield a positive predictive value of only 24–37%^{1, 2}, and up to 75% of these men have a negative first biopsy^{3, 4}. Furthermore, PCa is detected in 10–35% of men with negative first biopsy^{3, 4}. In clinical practice, it is often uncertain whether a repeat biopsy should be performed in men with clinically localized PCa and prior negative biopsy findings. In men with a negative first biopsy but persistently high PSA, the European Association of Urology (EAU)⁵ guidelines recommend a prostate biopsy; however, among men with suspicion of having PCa and a prior negative biopsy, a repeat biopsy was reported negative in approximately 80% of the men. In addition to being costly, biopsies are associated with morbidity, anxiety, discomfort and complications³. New biomarkers may increase the diagnostic accuracy of repeat biopsies, and reduce the number of unnecessary biopsies, but the long term health outcomes are unclear.

Results of recent studies have shown the potential clinical utility of the urine based PROGENSA prostate cancer antigen 3 (PCA3) assay to predict repeat biopsy outcomes in men with elevated serum PSA levels and previous negative biopsy findings^{6–15}, and reported that an increasing PCA3 score corresponds to an increasing probability of a positive repeat biopsy. The PCA3 test has been shown in some studies to be superior to serum PSA in predicting biopsy outcome^{6, 16, 17}, and has been included in recently developed nomograms^{18–20}. A recent literature review reported that current evidence suggests PCA3 is

clinically useful for selecting which patients should have a repeat biopsy²¹. Several studies have found that TMPRSS2:ERG (T2:ERG) is also associated with biopsy outcome^{22–28}, and may better discriminate between low and high grade cancers²². Although there are studies supporting increased diagnostic accuracy for both biomarkers, the ideal thresholds to trigger a repeat biopsy, and the resulting increase in survival and decrease in unnecessary biopsies are unknown.

We used decision analysis to evaluate the clinical value of PCA3 and T2:ERG in men with clinically localized PCa who had at least one prior negative biopsy. We performed head-to-head comparisons of protocols that use either PCA3 or T2:ERG in combination with PSA in terms of the incremental change in 10-year overall survival and the rate of negative biopsies. Furthermore, we considered 15-year cancer-specific survival as an endpoint in our analyses. We present results for both expected 10-year survival and 15-year cancer specific survival and the rate of repeat biopsy for each biomarker. We also present results of sensitivity analysis of clinical factors such as PSA level, biopsy detection rate and age to provide evidence about which patients benefit most from the use of an additional biomarker.

MATERIAL AND METHODS

Study population

The decision analysis model was based on the results from a prospectively collected cohort design. For the study cohort, post-DRE urine was prospectively collected from 1,977 men presenting for diagnostic prostate biopsy at three U.S. academic institutions (n= 733) and 7 community clinics (n= 1,244). The vast majority of men had elevated serum PSA. As this cohort reflects actual clinical practice, no specific indication for repeat biopsy was required; however the vast majority was for persistently elevated serum PSA. Exclusion criteria included the following: prior attempted curative therapy (radical prostatectomy (RP), radiation therapy (RT), androgen deprivation therapy (ADT) or brachytherapy), surgical treatment of the prostate within 6 months of urine collection (or previous biopsy within 6 weeks), taking 5 α -reductase inhibitors or testosterone within 3 months of urine collection, or prostatitis at the time of urine collection. All urine specimens were obtained with institutional review board approval.

Specimen collection and processing: Urine T2:ERG and PCA3 assay procedure

Urine processing for determination of PCA3 and T2:ERG scores was performed as described in prior studies^{22, 23, 29}. Urine specimens were obtained immediately after attentive DRE, refrigerated, and processed within 4 hours by mixing with an equal volume of urine transport medium and stored below –70°C until analysis. Amounts of urine PCA3, T2:ERG and PSA mRNA were determined with transcription mediated amplification (TMA) assays. To generate a T2:ERG score, the amount of T2:ERG mRNA is normalized to the amount of PSA mRNA, which is calculated using the following formula: $(100,000 \times \text{average urine TMPRSS2:ERG copies/mL}) / (\text{average urine PSA copies/mL})$. Samples with average urine PSA copies/mL of more than 10,000 copies/mL were considered informative for urine T2:ERG scores. Urine T2:ERG scores were assessed as described using the final T2:ERG

TMA assay as described in ^{23, 27, 29} or an earlier generation assay ²² that yield equivalent T2:ERG scores.

The PROGENSA PCA3 assay similarly quantitates PCA3 and PSA mRNA in post-DRE urine. The PCA3 score was calculated with the following formula: $1,000 \times (\text{average urine PCA3 copies/mL})/(\text{average urine PSA copies/mL})$. Samples with average urine PSA copies/mL of more than 10,000 copies/mL were considered informative. Identical primers for quantifying urine PSA are used in the PROGENSA PCA3 assay and T2:ERG assay.

All urine PCA3 and T2:ERG analysis was performed at the University of Michigan or Gen-Probe, Inc, with a subset of samples assessed at both to ensure concordance. A total of 1,936 urine samples had sufficient urine PSA (>10,000 copies/mL) to provide informative PCA3 and T2:ERG scores, and these samples were considered for analysis. The final study population consisted of 140 men with informative urine PCA3 and T2:ERG scores who had a history of at least one negative previous biopsy and were diagnosed with prostate cancer in their study biopsy.

Decision tree

We constructed a decision tree to compare the expected 10-year survival and 15-year cancer-specific survival for protocols that use one of the urinary biomarkers versus those that do not for patients with elevated PSA. The complete decision tree schema is shown in Figure A.1 in the online supplement. The initial decision is whether to use an additional biomarker (yes or no); if no additional biomarker is used then we considered two cases: repeat biopsy and no repeat biopsy. Therefore the decision tree has three separate separate decision branches.

Branch 1 represents the protocols that incorporate a urinary biomarker into repeat biopsy decisions. *Branch 2* represents the protocol that does not involve any additional indication for repeat biopsy, therefore every patient is assumed to receive biopsy regardless of his clinical parameters (age, serum PSA level etc.). *Branch 3* represents the protocol that no patient receives a repeat biopsy.

In the decision tree, men with detected and undetected clinically localized prostate cancer are assumed to have 10-year survival consistent with men who receive radical prostatectomy at diagnosis and men under conservative treatment (whose cases were managed without surgery or radiation), respectively. Although the decision tree focuses on a one-time repeat biopsy decision, the occurrence of delayed biopsy, histological reclassification, and future treatment are reflected in the survival estimates. The risk of prostate cancer was derived from the PCPTRC version 2.0 risk calculator, which incorporates age, race, PSA level, family history of prostate cancer, digital rectal examination and history of a negative biopsy ³⁰. The decision tree accounts for the different cancer grades based on patient's Gleason score (GS) (GS<7, GS=7, and GS>7). The probability for each grade was estimated based on the proportion of each outcome in the study population.

The biopsy decision *in Branch 1* of the decision tree is determined by a pre-specified threshold for the urinary biomarker. The probability that the biomarker score exceeds this threshold is grade dependent and estimated from the study population (See Table A.1 in the online supplement). The probability of a positive repeat biopsy was estimated from Haas et

al.³¹. The primary end point of each branch is the 10-year overall survival estimated from Tewari et al.³², which depend on cancer grade, age, serum PSA level, race and Charlson comorbidity index (CCI). We did not have CCI for the patients included in our study; thus, we assumed that they are healthy patients with CCI in the range of 0–1. Outcomes for patients without PCa were also taken from Tewari et al.³². The look-up tables for 10-year overall survival are constructed separately for black and white males; however, Tewari et al.³² did not find race to be an independent predictor of survival, and most of the patients in our study population were white. Thus, we considered the 10-year overall survival estimates in white males with clinically localized PCa.

We conducted similar analyses using the 15-year prostate cancer-specific survival as the primary end point in the decision tree. We used cancer-specific survival since there is no study in literature that estimates 15-year overall survival. We obtained the 15-year cancer-specific survival estimates for untreated, clinically localized PCa, from Johansson et al.³³, and the 15-year cancer-specific survival estimates after radical prostatectomy from Stephenson et al.³⁴.

There is no consensus about the most appropriate threshold for the PCA3 and T2:ERG tests. The FDA recommends a PCA3 threshold of 25, but a threshold of 35 is commonly used^{6–8, 15, 33–36}. While some studies have found the cutoff of 25 provides a good balance between sensitivity and specificity^{37–40}, others have supported the use of different thresholds, e.g. 17^{18, 19, 43} and 51²⁰. In this study we considered the thresholds of 25, 35 and 100 for PCA3. Regarding the T2:ERG threshold, Tomlins et al.²² considered the specimens with T2:ERG score >50 as positive, and Leyten et al.²⁸ considered the threshold of 10 in their multivariate regression analysis. In this study, to provide a diverse set of thresholds, we considered the thresholds of 7, 10, 30, 50 and 100.

Survival estimates

We conducted a literature review to obtain estimates of overall survival in clinically localized prostate cancer patients. Relevant studies were based on retrospective cohorts not screened by PSA that report survival outcomes in men with clinically localized PCa. Several use nomograms (for example, Cowen et al.⁴²) that could not be adapted to our study because complete information for all clinical variables was not available for the study cohort. Some, such as Walz et al.⁴³, lacked clinicopathological information, which was used in our analysis. Albertsen et al.⁴⁴ reported survival outcomes but the study considered men older than 66 years, and 38% of our study population is under age 66 years. Therefore, for our analysis, we used the overall 10-year survival estimates reported by Tewari et al.³², which quantify the impact of treatment modality on overall-survival of men with clinically localized PCa.

15-year survival estimates from Johansson et al.³³ were based on a cohort of patients with early, untreated PCa before the PSA screening era and are given for grade 1,2 and 3 cancers according to the World Health Organization (WHO) classification of malignant diseases. As noted by Johansson et al., we translated grade 1 to GS 2–4, grade 2 to GS 5–7 and grade 3 to GS 8–10 cancers. 15-year cancer-specific post-prostatectomy survival estimates from Stephenson et al.³⁴ were derived from a study cohort of patients who underwent radical

prostatectomy for localized prostate cancer in the era of PSA screening and given by GS <7, =7 and >7. We assumed that 15-year survival without PCa is same as the 15-year cancer-specific survival for GS 2–4 cancers estimated from Johansson et al.³³. Additional details about the analysis are given in the online supplement.

Probabilistic sensitivity analyses

We conducted multi-way probabilistic sensitivity analyses around model parameters (biopsy sensitivity, sensitivity of biomarkers at different thresholds for different cancer grades and 10-year survival under different treatments) and clinical parameters (serum PSA and age). We did not conduct multi-way sensitivity analyses representing the uncertainty around clinical parameters in the analysis of 15-year cancer-specific survival since the 15-year survival estimates are not available by PSA and age. Additional details about the ranges and assumed distributions are provided in online supplement. We sampled the parameters 1,000 times drawn from independent distributions and computed the additional 10-year survival and percentage of men biopsied for each resulting decision tree. We chose 4 and 30 ng/ml, and 50 and 75 years as lower and upper bounds on serum PSA and age, respectively.

RESULTS

Study population

Table 1 provides the characteristics of the 420 men who had previous negative biopsies. Men with a positive biopsy had a statistically significant higher age, lower prostate volume, and a higher mean PCA3 and T2:ERG scores than men with a negative repeat biopsy. Mean serum PSA did not significantly change between men with negative versus positive biopsy. Men with a positive biopsy had clinical stage T1 and T2 in 78.6% and 20% of cases, respectively; 88.6% had a biopsy Gleason score of 6–7 and 75% had 33% positive cores.

Additional details of the study population are provided in the online supplement. Table A.1 provides our estimates of the probability that a man's biomarker scores exceed different thresholds, based on the man's grade of PCa. Among 420 men with stage T1 or T2 prostate cancer, 140 (33.3%) had cancer on repeat biopsy. Of the 140 men with positive repeat biopsy, 82 (58.6%) had GS <7 cancer, 42 (30.0%) had GS =7 and 16 (11.4%) had GS >7 cancer. Based on univariate analysis, all of the pre-biopsy clinical variables were associated with a positive repeat biopsy ($p < 0.04$) (data not shown). PCA3 demonstrated the highest accuracy in predicting the positive repeat biopsy (AUC: 0.652), compared to the PSA (AUC: 0.54) in Table A.2.

Table A.3 shows PCa detection rates for varying PSA, PCA3 and T2:ERG thresholds, the number of prostate biopsies that would be avoided and PCa cases with GS 7 that would be missed if the urinary biomarker (PCA3 or T2:ERG) was used to select men for repeat biopsies. A PCA3 threshold 25 and 35 would detect 95 (67.9%) and 69 (49.3%) of PCa cases, respectively. A T2:ERG threshold 7 and 10 showed similar performance detecting 78 (55.7%) and 71 (50.7%) of PCa cases, respectively. A PCA3 threshold 25 would identify 42 (72.4%) of 58 cancer cases with GS 7 and avoid 52.4% of repeat biopsies, and a threshold of 35 would identify 32 (55.2%) cancer cases with GS 7, but 66.4% of all

biopsies could have been avoided. Similarly, a T2:ERG threshold ≥ 7 would identify 35 (60.3%) of 58 cancer cases with GS ≥ 7 and avoid 56.2% of repeat biopsies, and a threshold of ≥ 10 would identify 33 (56.9%) cancer cases with GS ≥ 7 , but 62.1% of all biopsies could have been avoided.

Base case analysis

We considered a base case patient with the following characteristics: white, age 65 years, most recent serum PSA of 6.3 ng/ml based on the mean PSA of patients in the study cohort, CCI of 0, no family history of prostate cancer, normal DRE and a prior negative biopsy. Table 2 presents 10-year survival and biopsy rates for the protocols with varying biopsy thresholds. Table 2 shows that *Branch 2* (repeat biopsy) yields better 10-year survival than *Branch 1* (biomarker at repeat biopsy) under every protocol with various PCA3 and T2:ERG thresholds. Similar results were obtained in the analysis of 15-year cancer-specific survival (See Table A.4 in the online supplement).

Probabilistic sensitivity analyses

Multi-way probabilistic sensitivity analyses consisted of two steps. The first step involved varying the model parameters. The results summarized in Table 3 show that the confidence interval for each protocol is relatively narrow, and the magnitude of effect difference for each protocol was not changed when uncertainty was incorporated for the base case patient. In second step, we performed a sensitivity analysis including the uncertainty around serum PSA level and age of the base case patient in addition to varying the model parameters (Table 4). Multi-way sensitivity analyses demonstrated that *Branch 2* (repeat biopsy) yields better 10-year survival than *Branch 1* (biomarker at repeat biopsy) under every protocol with various PCA3 and T2:ERG thresholds. Similar results were obtained in the analysis of 15-year cancer-specific survival (See Table A.5 in the online supplement).

DISCUSSION

There is no definitive criterion to decide whether to perform a repeat prostate biopsy. Typically the decision to perform a repeat biopsy is based on the measurement of serum PSA and the findings of a DRE. The use of diagnostic biomarkers such as PCA3 and T2:ERG may help clinicians make better decisions about repeat biopsies. In this respect, the PCA3 assay and T2:ERG have shown promising results, and the studies available in the literature support the use of PCA3 in patients with persistent suspicions of PCa who had undergone previous negative biopsies. However, these studies focus on diagnostic performance and not health outcomes. In this study, we investigated the value of PCA3 and T2:ERG for improving the overall 10-survival and reducing unnecessary repeat biopsies in the challenging subgroup of patients with previous negative biopsies and persistently elevated PSA levels.

Based on multi-way sensitivity analysis for the base case patient, the protocols using a PCA3 threshold of ≥ 25 and a T2: ERG threshold of ≥ 10 at repeat biopsy decisions resulted in a 54.4% and 63.2% reduction in the total number of biopsies performed compared to the protocol that every man with suspicion of PCa is biopsied, while the loss in 10-year survival

was 0.9% and 1.4%, respectively. Multi-way sensitivity analyses varying base case patient's age and serum PSA level in addition to varying the model parameters demonstrated that incorporating PCA3 or T2:ERG into repeat biopsy decisions provided a large reduction in the total number of biopsies (53.2% and 62.0% with a PCA3 threshold of 25 and T2:ERG threshold of 10, respectively) and resulted in a small change (<2.1%) in 10-year overall survival compared to the case where every man was biopsied. The reduction in number of biopsies increased as the threshold for biomarkers increased, while the loss in 10-year survival also increased slightly. In the analysis of 15-year cancer-specific survival, multi-way sensitivity analysis for the base case patient showed that the protocols using a PCA3 threshold of 25 and a T2:ERG threshold of 10 at repeat biopsy decisions resulted in a loss in 15-year cancer-specific survival of 1.5% and 2.5%, respectively. Similar to 10-year overall survival analysis, the reduction in number of biopsies increased as the threshold for biomarkers increased, while the loss in 15-year cancer-specific survival also increased slightly.

Our study did not address cost implications of the protocols incorporating biomarkers into repeat biopsy decisions. Some insight can be gained by considering the cost of biomarkers and biopsy in *Branch 1* of the decision tree. The cost of biopsy and a PSA test are approximately, \$904⁴⁷ and \$31⁴⁸, respectively. There is no established independent cost for T2:ERG; therefore, we assumed that the institutional costs of PCA3 and T2:ERG markers are the same, and we used the bundled cost of \$749 for Mi-Prostate Score (MiPS), which is an early detection test for PCa that combines PSA, PCA3 and T2:ERG⁴⁹. Based on these cost estimates, the expected cost of using PCA3 with a threshold of 25 and T2:ERG with threshold of 10 are \$782 and \$753, respectively, compared to \$904 for *Branch 2* in the decision tree.

This study has some limitations. We examined a relatively small proportion of patients with clinically insignificant PCa. This raises the question whether our study consists of a representative cohort. However, we need to emphasize that the data was prospectively collected from multiple centers, thus selection-bias is minimal. Additional limitations of this study are related to model inputs such as 10-year survival and 15-year cancer-specific survival estimates and biopsy sensitivity. The limitations of the studies providing estimates of overall survival include the nonrandomized treatment assignment and retrospective design. The studies evaluated overall survival within 10 years of treatment. A cohort of patients with longer follow-up (more than 10 years) would provide more accurate estimates of long term outcomes. We assumed that the overall survival is independent of the biomarker test scores since there is no study that provides survival estimates considering PCA3 and T2:ERG test results. An alternative would be to base the model on expected lifespan, or quality adjusted lifespan, rather than survival; however, such considerations would require a Markov model which would require many assumptions about follow-up to the repeat biopsy decision.

These limitations notwithstanding, our study has several strengths, as well as important clinical and policy implications regarding the application of PCA3 assay and T2:ERG in repeat biopsy decisions. We performed a head-to-head comparison of these biomarkers in providing supplementary information to guide repeat biopsy decisions, and found that the

PCA3 assay and T2:ERG appear to provide an incremental improvement in the ability to increase the specificity while resulting in a slight decrease in the overall 10-year survival relative to the case where every men is biopsied regardless of the clinical parameters. In addition to the effect on healthcare usage, avoiding unnecessary repeat biopsies will reduce the discomfort, pain, and the other complications associated with repeat biopsies.

CONCLUSIONS

The present study investigated, for the first time, the value of PCA3 and T2:ERG in the diagnosis of PCa at repeat biopsy by comparing the loss in the overall survival to the gain in repeat biopsy rate. The results from this study suggest that PSA alone is ineffective for recommending patients have a repeat biopsy after previous negative biopsies. The addition of PCA3 or T2:ERG for repeat biopsy decisions can reduce the number of biopsies substantially; however, this is associated with some reduction in 10-year overall survival and 15-year cancer-specific survival. Decisions about whether to use PCA3 or T2:ERG at repeat biopsy should weigh these competing considerations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of the study population

	Men with negative biopsy (n=280)	Men with positive biopsy (n=140)	p value	All men (n=420)
	Mean $\pm$ SD / number (%)	Mean $\pm$ SD / number (%)		Mean $\pm$ SD / number (%)
Age (years)	65.4 $\pm$ 8.1	68.2 $\pm$ 8.9	0.002 [*]	66.3 $\pm$ 8.5
Serum PSA (ng/ml)	7.2 $\pm$ 5.4	8.4 $\pm$ 6.5	0.0766 [°]	7.5 $\pm$ 5.8
Men with serum PSA (ng/ml) (%)				
<4	55 (19.6)	24 (17.1)		79 (18.8)
4–10	177 (63.2)	83 (59.3)		260 (61.9)
>10	48 (17.1)	33 (23.6)		81 (19.3)
No. Ethnicity (%)			0.0113 [§]	
African-American	12 (4.3)	15 (10.7)		27 (6.4)
Other	268 (95.7)	125 (89.3)		393 (93.6)
No. DRE result			0.0783 [§]	
Normal	242 (86.4)	110 (78.6)		352 (83.8)
Abnormal	33 (11.8)	28 (20.0)		61 (14.5)
Not available	5 (1.8)	2 (1.4)		7 (1.7)
Prostate volume (n=273/136/409)	69.3 $\pm$ 39.8	58.2 $\pm$ 33.1	0.0016 [°]	65.6 $\pm$ 38.0
PCA3 score	32 $\pm$ 36.4	61 $\pm$ 78.4	<0.0001 [°]	41.7 $\pm$ 55.8
T2:ERG score	32.8 $\pm$ 110.4	127.5 $\pm$ 678.3	0.0006 [°]	64.4 $\pm$ 403.4

Abbreviations: SD, Standard deviation; PSA, Prostate-specific antigen; DRE, digital rectal examination; PCA3, Prostate Cancer Antigen 3, T2:ERG, the transmembrane protease, serine 2 (TMPRSS2); v-ets erythroblastosis virus E26 oncogene homolog (avian) (ERG) fusion.

^{*} t-test,

[°] Wilcoxon rank sum test,

[§] χ^2 test.

Table 2

10-year life survival and percentage of men biopsied for the base case patient at various biopsy thresholds for PCA3 and T2:ERG

Biomarkers at different thresholds	Percentage of men biopsied at this threshold	10-year survival	Percentage change in survival [*]	Percentage change in survival [°]
Branch 1[§]				
PCA3				
25	44.63	83.98	0.93 (0.66, 1.14)	2.00 (1.42, 2.45)
35	31.25	83.44	1.47 (1.04, 1.78)	1.46 (1.04, 1.79)
T2:ERG				
7	42.05	83.63	1.27 (0.91, 1.56)	1.65 (1.17, 2.03)
10	35.95	83.50	1.41 (1.00, 1.73)	1.51 (1.07, 1.86)
30	23.70	83.03	1.88 (1.33, 2.30)	1.05 (0.75, 1.29)
50	19.28	83.84	2.07 (1.47, 2.53)	0.86 (0.61, 1.06)
100	10.11	82.54	2.36 (1.68, 2.90)	0.57 (0.40, 0.70)
Branch 2[†]	100.0	84.91	-	-
Branch 3^β	0.0	81.98	-	-

[§] *Branch 1* uses urinary biomarkers at repeat biopsy;

[†] *Branch 2* has no indication at repeat biopsy;

^β *Branch 3* is no repeat biopsy;

^{*} This is the absolute difference between *Branch 1* and *Branch 2*,

[°] This is the absolute difference between *Branch 1* and *Branch 3*.

The numbers in the parentheses are calculated using the 95% Confidence Intervals estimated by Tewari et al.³² on the 10-year survival under radical prostatectomy and conservative management.

Table 3

Multi-way probabilistic sensitivity analysis representing the uncertainty around model parameters

Biomarkers at different thresholds	Percentage of men biopsied at this threshold, (95% CI)	10-year survival	Percentage change in survival [*] , (95% CI)	Percentage change in survival [°] , (95% CI)
Branch 1[§]				
PCA3				
25	45.46 (44.91 – 46.01)	83.91 (83.83 – 84.00)	0.92 (0.91 – 0.94)	1.99 (1.96 – 2.01)
35	32.36 (31.92 – 32.79)	83.38 (83.30 – 83.47)	1.45 (1.43 – 1.48)	1.45 (1.43 – 1.48)
T2:ERG				
7	42.82 (42.29 – 43.35)	83.57 (83.48 – 83.65)	1.27 (1.25 – 1.29)	1.66 (1.63 – 1.68)
10	36.79 (36.35 – 37.30)	83.43 (83.35 – 83.52)	1.40 (1.38 – 1.42)	1.52 (1.50 – 1.54)
30	24.59 (24.23 – 24.95)	82.97 (82.89 – 83.05)	1.87 (1.84 – 1.89)	1.05 (1.04 – 1.07)
50	21.93 (21.60 – 22.27)	82.79 (82.71 – 82.87)	2.05 (2.02 – 2.07)	0.86 (0.85 – 0.88)
100	8.54 (8.74 – 8.35)	82.50 (82.41 – 82.58)	2.34 (2.31 – 2.37)	0.58 (0.57 – 0.59)
Branch 2[†]	100.0	84.84 (84.75 – 84.93)	-	-
Branch 3^β	0.0	81.93 (81.84 – 82.01)	-	-

[§] *Branch 1* uses urinary biomarkers at repeat biopsy;[†] *Branch 2* has no indication at repeat biopsy;^β *Branch 3* is no repeat biopsy;^{*} The difference is calculated as the absolute difference between *Branch 1* and *Branch 2* in the decision tree;[°] The difference is calculated as the absolute difference between *Branch 1* and *Branch 3* in the decision tree.

Table 4

Multi-way probabilistic sensitivity analyses representing the uncertainty around model and clinical parameters (serum PSA and age)

Biomarkers at different thresholds	Percentage of men biopsied at this threshold, (95% CI)	10-year survival	Percentage change in survival [*] , (95% CI)	Percentage change in survival ^o , (95% CI)
Branch 1[§]				
PCA3				
25	46.80 (46.27 – 47.32)	82.16 (81.72 – 82.61)	1.36 (1.31 – 1.42)	2.92 (2.82 – 3.03)
35	33.53 (33.10 – 33.96)	81.38 (80.92 – 81.85)	2.14 (2.22 – 2.06)	2.14 (2.06 – 2.22)
T2:ERG				
7	43.55 (43.04 – 44.07)	81.65 (81.19 – 82.11)	1.88 (1.81 – 1.95)	2.41 (2.32 – 2.50)
10	37.99 (37.51 – 38.47)	81.44 (80.98 – 81.91)	2.09 (2.01 – 2.17)	2.20 (2.12 – 2.28)
30	25.47 (25.12 – 25.83)	80.77 (80.29 – 81.26)	2.75 (2.65 – 2.86)	1.53 (1.48 – 1.59)
50	22.66 (22.34 – 22.98)	80.49 (80.00 – 80.98)	3.04 (2.92 – 3.15)	1.25 (1.20 – 1.30)
100	9.34 (9.13 – 9.54)	80.07 (79.57 – 80.57)	3.46 (3.59 – 3.33)	0.83 (0.80 – 0.86)
Branch 2[†]	100.0	83.53 (83.12 – 83.94)	-	-
Branch 3^β	0.0	79.24 (78.71 – 79.77)	-	-

[§] Branch 1 uses urinary biomarkers at repeat biopsy;

[†] Branch 2 has no indication at repeat biopsy;

^β Branch 3 is no repeat biopsy;

^{*} The difference is calculated as the absolute difference between Branch 1 and Branch 2 in the decision tree.

^o The difference is calculated as the absolute difference between Branch 1 and Branch 3 in the decision tree.