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ORIGINAL REPORT

Prospective Multi-Institutional Study Evaluating the Performance of Prostate Cancer Risk Calculators

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ABSTRACT

Purpose
Prostate cancer risk calculators incorporate many factors to evaluate an individual's risk for prostate cancer. We validated two common North American–based, prostate cancer risk calculators.

Patients and Methods
We conducted a prospective, multi-institutional study of 2,130 patients who underwent a prostate biopsy for prostate cancer detection from five centers. We evaluated the performance of the Sunnybrook nomogram–based prostate cancer risk calculator (SRC) and the Prostate Cancer Prevention Trial (PCPT) –based risk calculator (PRC) to predict the presence of any cancer and high-grade cancer. We examined discrimination, calibration, and decision curve analysis techniques to evaluate the prediction models.

Results
Of the 2,130 patients, 867 men (40.7%) were found to have cancer, and 1,263 (59.3%) did not have cancer. Of the patients with cancer, 403 (46.5%) had a Gleason score of 7 or more. The area under the [concentration-time] curve (AUC) for the SRC was 0.67 (95% CI, 0.65 to 0.69); the AUC for the PRC was 0.61 (95% CI, 0.59 to 0.64). The AUC was higher for predicting aggressive disease from the SRC (0.72; 95% CI, 0.70 to 0.75) compared with that from the PRC (0.67; 95% CI, 0.64 to 0.70). Decision curve analyses showed that the SRC performed better than the PRC for risk thresholds of more than 30% for any cancer and more than 15% for aggressive cancer.

Conclusion
The SRC performed better than the PRC, but neither one added clinical benefit for risk thresholds of less than 30%. Further research is needed to improve the AUCs of the risk calculators, particularly for higher-grade cancer.

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INTRODUCTION

The results of randomized studies that evaluate the efficacy of prostate cancer screening that uses the prostate-specific antigen (PSA) test highlight the need to reduce the overdiagnosis of patients with indolent and nonaggressive forms of prostate cancer.[1,2] New approaches are needed to better select patients who are at increased risk for having prostate cancer, particularly the aggressive, high-grade forms.

The use of prostate cancer risk calculators for deciding whom to biopsy has been demonstrated to be superior to conventional decision making based on PSA and digital rectal examination (DRE).[3,4] The Prostate Cancer Prevention Trial (PCPT) showed that age, family history of prostate cancer, ethnicity, and DRE results increased the positive predictive value of PSA and developed an online prostate cancer risk calculator (PRC) based on these factors.[4] Our group developed a Sunnybrook nomogram–based online prostate cancer risk calculator (SRC) that estimates an individual's risk for any prostate cancer and high-grade prostate cancer.[3] We showed that the combination of age, family history of prostate cancer, ethnicity, urinary voiding symptom score, DRE, PSA, and free:total PSA ratio performed significantly better than conventional use of PSA and DRE in predicting the presence of prostate cancer.

To validate these prostate cancer risk calculators, we conducted a prospective, multi-institutional study that evaluated the performance of these instruments. We compared the ability of these prediction models with respect to their discrimination and calibration techniques[5] in predicting the presence of prostate cancer and aggressive, high-grade prostate cancer. We also performed decision curve analysis to compare the models.

PATIENTS AND METHODS

Study Patients

From 2007 to 2009, patients were prospectively assembled from five centers across Canada with large prostate biopsy cohorts: Sunnybrook Health Sciences Centre (n = 604), Toronto East General Hospital (n = 363), and Princess Margaret Hospital (n = 382) all in the Toronto area, and London Health Sciences Centre in London, Ontario (n = 420); and Victoria General Hospital, Halifax, Nova Scotia, Canada (n = 361).

Patients were eligible for inclusion if they had an abnormal PSA level (> 2.6 ng/mL) or an abnormal DRE test. All patients were offered a transrectal ultrasound-guided prostate biopsy. However, the probability for prostate cancer based on the prostate cancer risk calculators was not factored into the decision, and both patients and investigators were blinded to these estimates. All patients underwent transrectal ultrasound-guided needle core biopsy (10 to 12 needle core samples). Patients were excluded if their PSA level was more than 50 ng/mL, if the decision to biopsy would be considered unequivocal (n = 67), if they had incomplete risk factor information (n = 20), or if they were unable to provide consent (n = 10). Of the 2,227 total patients, 2,130 agreed to participate in the study.

Primary End Point and Baseline Information

The primary end point was the histologic presence of adenocarcinoma of the prostate biopsy specimen and aggressive cancer. All grading was based on the Gleason scoring system.[6] No central pathology review was obtained. However, each tertiary-based center was considered a referent prostate biopsy center. Biopsy samples from Toronto East General Hospital (a community-based hospital) were also reviewed by a referent prostate biopsy center.

Patient age at time of biopsy, urologic voiding history (American Urological Association [AUA] symptom score[7]), ethnic background, family history of prostate cancer, PSA level, free:total PSA ratio, and DRE results were obtained by questionnaires. These questionnaires were carefully and systematically administered by each center before prostate biopsy or knowledge of the primary end point. All data and follow-up information were assembled at each center by the designated principal investigator and then sent to a centralized

Table 1. Multivariable Logistic Regression Analysis of Factors Associated With Prostate Cancer

Factor	Cases No.	Cases %	Controls No.	Controls %	OR	95% CI	*P*
Age, years							
< 60	245	28	491	39	1.0		
60-70	412	48	572	45	1.4	1.1 to 1.7	.002
> 70	210	24	200	16	2.1	1.6 to 2.8	< .001
Family history of prostate cancer							
Absent	661	76	1,003	79	1.0		
Present	206	24	260	21	1.3	1.0 to 1.6	.02
Ethnicity							
Asian	42	5	137	11	1.0		
White	776	89	1,072	85	2.5	1.7 to 3.7	< .001
Black	49	6	54	4	3.3	1.9 to 5.7	< .001
Urinary symptoms by AUA symptom score*							
≤ 6	436	50	543	43	1.0		
> 6	431	50	720	57	0.7	0.6 to 0.8	< .001
DRE							
Normal	679	78	1,120	89	1.0		
Abnormal	188	22	143	11	2.6	2.0 to 3.4	< .001
PSA (ng/mL)							
< 2.6	32	4	167	13	1.0		
2.6-4.0	79	9	165	13	2.9	1.7 to 4.7	< .001
> 4.0-10.0	591	68	767	61	4.6	3.0 to 7.0	< .001
> 10.0	165	19	164	13	4.9	3.0 to 7.8	< .001
Free:total PSA†							
> 0.22	152	18	301	24	1.0		
0.16-0.22	137	16	303	24	0.9	0.6 to 1.1	.24
0.11-0.22	229	26	343	27	1.3	1.0 to 1.7	.07
< 0.11	349	40	316	25	2.0	1.5 to 2.6	< .001

Abbreviations: AUA, American Urological Association; DRE, digital rectal examination; OR, odds ratio; PSA, prostate-specific antigen.
*Based on AUA symptom score index from 0 to 35.
†Quartile of free:total PSA ratio based on the distribution of controls.

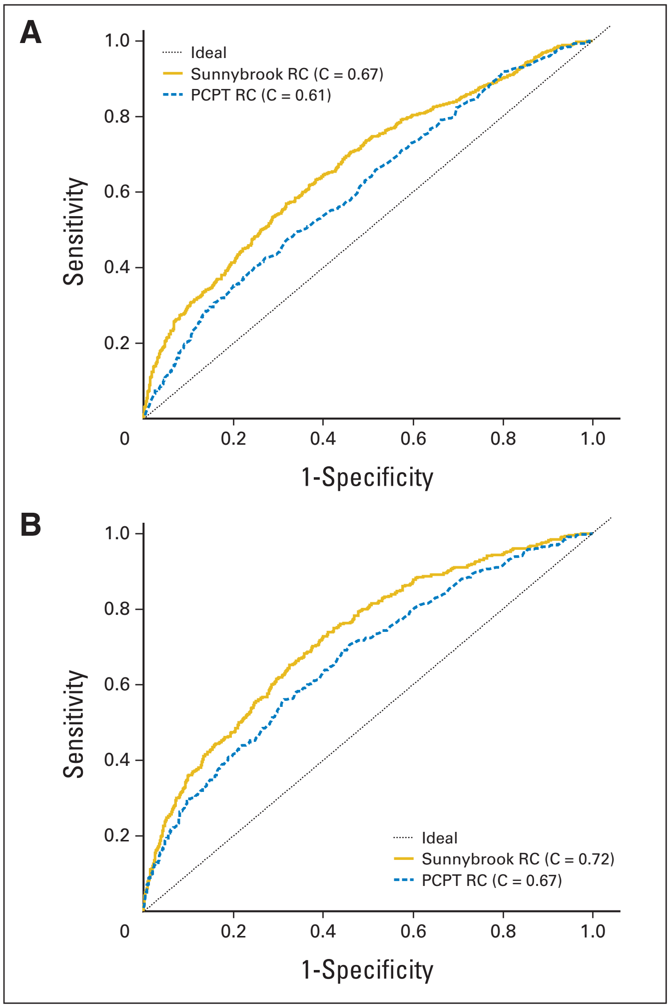

Fig 1. Receiver operating characteristic (ROC) curves in predicting the presence of all prostate cancer (A) and aggressive prostate cancer (B) by using the Sunnybrook risk calculator (RC) and the Prostate Cancer Prevention Trial (PCPT) RC. "C" refers to the concordance index, area under the ROC curve.

database. Random samples were chosen from each center and audited for data accuracy by the principal study team. Each center had approval from its respective research ethics board.

Data Analysis

The distributions of the baseline predictor variables were examined. Multivariable unconditional logistic regression was used to examine the association between predictor variables of age, family history of prostate cancer, ethnicity, the presence of urinary symptoms, PSA, free:total PSA ratio, and DRE.

To evaluate the performance of each prostate cancer risk calculator, we obtained the predicted probability for any prostate cancer and for aggressive prostate cancer for each patient from the PRC[4] (http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp) and from the SRC[3] (http://www.prostaterisk.ca) to evaluate each prediction model performance as established by Steyerberg et al.[5] Similar study patients with either a normal PSA level (< 4.0 ng/mL) or an abnormal PSA level (≥ 4.0 ng/mL) or DRE results were used to help develop the risk calculators. A random sample of 25% of the probabilities was reviewed to ensure accuracy of data entry. Each calculator provides probabilities for the presence of any cancer and aggressive cancer defined by a histologic grade of Gleason score 7 or more. We quantified the discrimination ability of the risk calculators by calculating the concordance index, which is identical to the nonparametric area under the receiver operating characteristic curve (AUC). It gives the probability that, in a randomly selected pair of patients in which one patient has prostate cancer and the other does not, the patient with prostate cancer will be assigned the worse predicted risk. It ranges from 0.5 (no discrimination) to 1 (perfect discrimination). To test the significance between the AUCs of the risk calculators, we created 2,000 concordance indices for each model by using bootstrapping analysis and then calculated the differences between the paired concordance indices. Significance was determined if the 2.5th quantile of the sorted difference was greater than zero.

We then compared the calibration of the two risk calculators by plotting the predictions on the *x*-axis and the observed outcomes on the y-axis in the same plot. In the calibration plot, the 45-degree line represents the perfect predictions. Because of binary outcomes, a smoothing technique was used to generate the observed probabilities of prostate cancer on the y-axis. Finally, we conducted a decision curve analysis that was proposed by Vickers et al[8] to assess the clinical usefulness of the prediction tools by quantifying the net benefits when different threshold probabilities were considered. All statistical analyses were performed by using R version 2.9.0 (http://www.R-project.org) with the Design and Hmisc libraries added.

RESULTS

Of 2,130 men, the median PSA level was 5.7 ng/mL (interquartile range, 4.2 to 8.1 ng/mL), and 331 men (15.5%) had an abnormal DRE. The median age at biopsy was 63 years (interquartile range, 58.0 to 69.0 years). In addition, 466 (22%) had a positive family history of prostate cancer. The majority of patients were white (87%; n = 1,848), with 8% (n = 179) having an Asian background and 5% (n = 103) having African ancestry. Of the 443 patients with a PSA level less than 4.0 ng/mL, 343 (77%) had a normal DRE.

A total of 867 men (41%) were found to have prostate cancer at biopsy (cases), and 1,263 (59%) had no evidence of cancer (controls). Of the patients with cancer, 464 (54%) had a histologic grade of Gleason score 6, 235 (27%) had Gleason score 7, and 168 (19%) had Gleason score 8 to 10. All of the factors that our earlier studies confirmed were significantly associated with prostate cancer risk, including age, family history of prostate cancer, ethnicity, urinary voiding symptoms, PSA, free:total PSA ratio, and DRE were also significant predictors for prostate cancer (Table 1).

To quantify the discrimination ability of the risk calculators among the 2,130 men, we examined the concordance index (AUC) for each model in predicting any cancer and high-grade, aggressive cancer (Gleason score 7 or higher). The AUC for the SRC (0.67; 95% CI, 0.65 to 0.69) in predicting prostate cancer was significantly higher than that for the PRC (0.61; 95% CI, 0.59 to 0.64; $P = .001$ for comparison). The AUC was also higher for predicting aggressive disease for the SRC (0.72; 95% CI, 0.70 to 0.75) compared with the PRC (0.67; 95% CI, 0.64 to 0.70; $P = .001$ for comparison; Fig 1). When we compared the sensitivity, specificity, positive predictive value, and negative predictive value for predicting any cancer, the risk calculators appeared to have similar test characteristics over a range of nomogram probabilities for predicting any cancer (Table 2). For predicting aggressive prostate cancer, the SRC appeared to have better sensitivity and negative predictive value for the low threshold range (Table 2).

Table 2. Sensitivity, Specificity, PPV, and NPV for the Risk Calculators for a Range of Probability Thresholds for Prostate Cancer

	Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
Nomogram Probability (%)	SRC	PRC	SRC	PRC	SRC	PRC	SRC	PRC
Test Characteristics for Predicting Any Cancer								
10	100	100	1	1	41	43	90	83
15	98	99	8	2	42	43	86	82
25	83	98	34	6	46	44	74	82
40	54	77	70	35	55	47	69	67
50	37	48	83	67	60	52	66	63
75	8	6	99	98	82	69	61	58
Test Characteristics for Predicting Aggressive Cancer								
10	94	83	23	34	22	24	94	89
15	82	66	47	57	27	28	92	87
25	56	41	75	75	34	35	88	84
40	30	22	93	94	49	47	85	83
50	17	12	97	97	55	57	83	82
75	2	4	100	100	77	78	81	80

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; PRC, Prostate Cancer Prevention Trial (PCPT)–based risk calculator; SRC, Sunnybrook nomogram–based prostate cancer risk calculator.

To assess the agreement between the predicted and actual outcomes, we generated calibration curves for each risk calculator for any and high-grade cancer. When compared with the ideal curve (45-degree line) in which there was perfect agreement between the predicted and actual outcomes, the SRC was closer than the PRC for both any and aggressive cancer (Fig 2).

Because there is no established cutoff probability for the prostate cancer risk calculators, we examined the theoretical relationship between a range of threshold probabilities for cancer in how it affects the relative value of false-positive and false-negative results (termed net benefit) by using decision curve analysis described by Vickers et al.[8] When compared with a theoretical scenario of performing a prostate biopsy for every patient, the ability of both risk calculators to predict cancer provided a better net benefit over a range of threshold probabilities for any and aggressive prostate cancer (Fig 3). The risk calculators did not provide further benefit compared with a scenario of conducting a biopsy for all patients for threshold probabilities of ≤ 30% for any cancer and ≤ 15% for aggressive cancer. The risk calculators also did not provide further

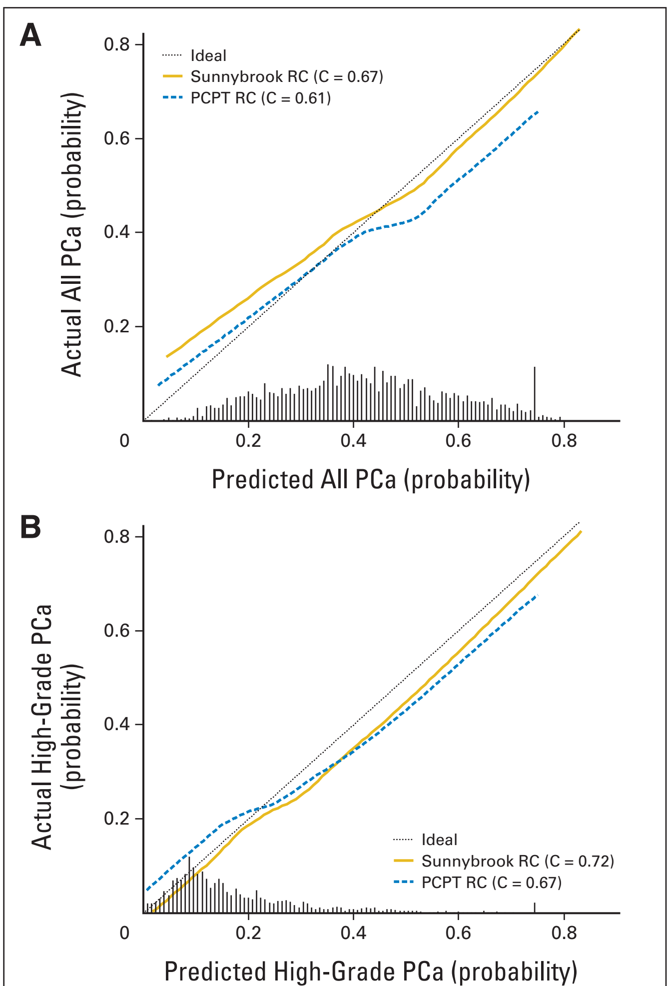

Fig 2. Calibration curve comparisons between the Prostate Cancer Prevention Trial (PCPT) –based and Sunnybrook nomogram–based prostate cancer (PCa) risk calculators (RCs) for any cancer (A) and high-grade, aggressive cancer (B). The *y*-axis represents observed prostate cancer rate. Diagonal black 45-degree dotted line represents perfect prediction by ideal model. "C" refers to the concordance index, area under the receiver operating characteristic curve. The histograms represent the predicted probabilities of the models that display the density distribution of predicted risks. Because the histograms were constructed on the basis of the density distribution instead of the absolute frequency of each predicted risk, the relative frequency can be observed.

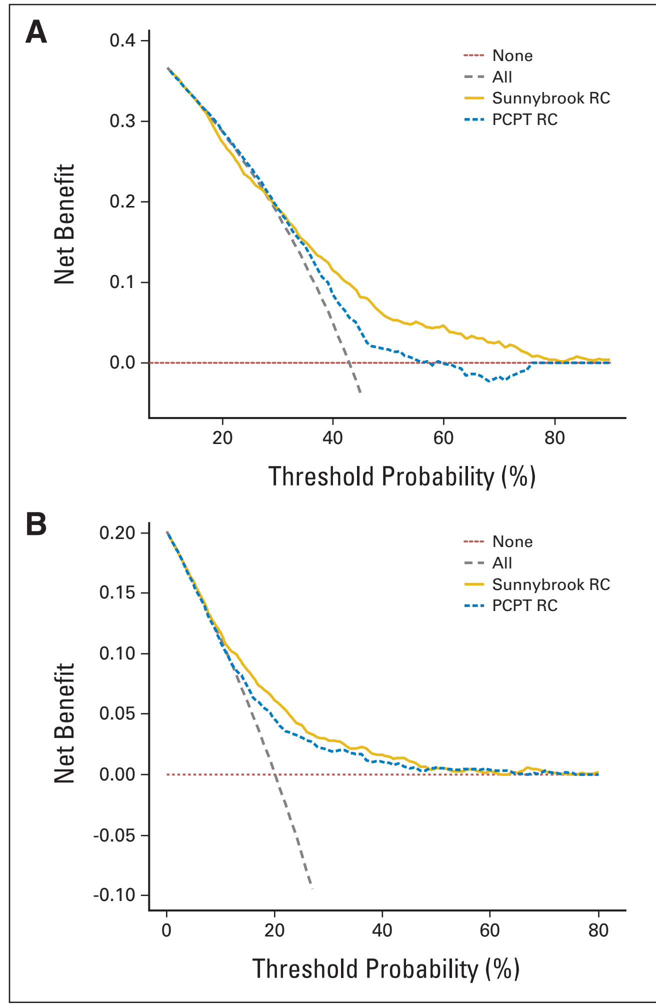

Fig 3. Decision curve analysis for prostate cancer biopsy prediction for each model for any cancer (A) and high-grade, aggressive cancer (B). The *y*-axis measures net benefit, calculated by summing the benefits (true positives) and subtracting the harms (false positives), in which the latter are weighted by a factor related to the relative harm of a missed cancer compared with the harm of an unnecessary biopsy. A model is of clinical value if it has the highest net benefit compared with both other models and simple strategies such as biopsying all patients (gray dashed line) or no patients (horizontal red line) across the full range of threshold probabilities at which a patient would choose to be biopsied. The unit is in terms of cancers found: a model with a net benefit of 0.1 is the equivalent of a strategy that biopsied 10 men per 100 with no negative biopsies. For example, if we take a threshold probability of 40%, the use of the Prostate Cancer Prevention Trial (PCPT) risk calculator (RC; dashed blue line) as a strategy would equate to 0.08 of net benefit which translates to the identification and biopsy of eight men, all with cancer on biopsy, of 100 men eligible (with no negative biopsies). Of those same 100 men, the Sunnybrook RC would have a net benefit of 0.12, which means that it would identify 12 men, all with cancer with no negative biopsies. Thus, for a threshold probability of 40% to perform a prostate biopsy, the Sunnybrook RC would theoretically identify four more cases of prostate cancer per 100 men with no negative biopsies compared with the PCPT RC. The dashed blue and solid gold lines evaluate the performance of the RCs for various strategies over the wide spectrum of threshold probabilities to perform a prostate biopsy from the decision analytic model.

benefit compared with a scenario of not conducting a biopsy for all patients for threshold probabilities of more than 55% for any cancer and more than 40% for aggressive cancer. Within these probabilities ranges, the SRC provided better value in net benefit compared with the PRC (Fig 3).

DISCUSSION

To the best of our knowledge, this is the first study to prospectively validate the current and most widely used North American–based prostate cancer risk calculators among different centers. Among a new cohort of 2,130 men derived from multiple centers that underwent a prostate biopsy, the SRC performed better than the PRC in predicting the presence of any and aggressive prostate cancer.

Since the original publications of the risk calculators, many investigators have called for external validation of the risk calculators.[9] Several studies have examined the PRC with reported AUCs widely ranging from 0.57 to 0.67, likely due to their retrospective study designs.[10-13] The advantages of the current prospective study compared with past retrospective studies are that they are free from ascertainment and recall biases of the risk factors that are important to the predictor models, including family history of prostate cancer, ethnicity, and urinary voiding symptoms. Importantly, the decision to undergo a biopsy was not based on the risk calculators, which minimized potential selection biases.

The AUC (0.72) of the SRC for predicting aggressive, high-grade prostate cancer was higher compared with that for the PRC. Although the absolute level is low, this value is affected by many factors.[14] From a decision-making perspective, the comparison of options is what matters and selecting the most accurate calculator available. This superior predictive value of the SRC is likely due to the incorporation of additional factors including free:total PSA ratio and urinary voiding symptoms. We acknowledge that this validation study is limited to patients referred for a prostate cancer evaluation and may not reflect the general population for prostate cancer screening, as observed in our high cancer detection rate of 40%. Nevertheless, this cohort reflects a contemporary cohort of screened patients as reflected in a median PSA of 5.7 ng/mL and an abnormal DRE in only 15%.

Another limitation of the study was that there was no central pathology review. However, we chose only centers that were considered a referent genitourinary pathology site, which minimized interobserver variability.

The main clinical utility of prostate cancer risk calculators is to facilitate the decision on whether a patient requires a prostate biopsy. This depends on which threshold probability is used. It has been suggested that a range of threshold probabilities for cancer between 10% and 40% would determine the need for prostate biopsy.[15] That is, a risk of 10% for cancer would likely dissuade a patient from undergoing an invasive biopsy, although a risk of 40% would compel a patient to have a biopsy (especially if the risk was for high-grade cancer). By using this arbitrarily defined range, both risk calculators would not improve clinical outcome relative to biopsying all men with an increased PSA or abnormal DRE. From our results, our risk calculator (SRC) would have the most benefit in decision making for patients who require a 30% or greater risk of cancer before they would agree to a biopsy, or physicians who would do no more than three biopsies to find one cancer.

However, it is important to emphasize that there are no studies to date that have evaluated what would be an acceptable range of threshold probabilities that would help with prostate biopsy management. Although 10% to 40% appears reasonable, it is possible that patients and physicians may accept lower or higher risk thresholds, depending on how risk averse an individual would be. Results of the PCPT showed a prevalence of prostate cancer of 15% among patients in the placebo arm with a normal PSA who underwent an end-of-study biopsy,[16] which could serve as a baseline risk for prostate cancer. In the absence of definitive risk thresholds, it would be important to provide a range of threshold probabilities, although extreme ranges would not be helpful. The decision analytic curves (Fig 3) show that the SRC in the range of these probabilities was consistently better in net benefit than the PRC (Fig 3), particularly for predicting aggressive, high-grade cancer. An individual patient can receive a different message when using the more accurate SRC relative to the PRC.

The method of decision analytic curves is novel and is used to address the problems of current methods of how we evaluate diagnostic tests. A limitation of the decision analytic curves is that the concept of net benefit is difficult to apply clinically since it is a mathematically derived definition. Another limitation is that decision curve analysis does not help decide which probability threshold should be considered acceptable. Nonetheless, the analysis provides a relative comparison between predictive models to assess how they perform within the spectrum of being either all positive or all negative predictions.

Thus, the SRC can be considered by physicians and patients who are considering undergoing a prostate biopsy to determine the presence of prostate cancer. Given the importance of selectively identifying men with aggressive, high-grade cancer, prostate cancer risk calculators can play an important role in prostate biopsy decision making. Further research will be required to evaluate what risk thresholds would be acceptable for patients and physicians.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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