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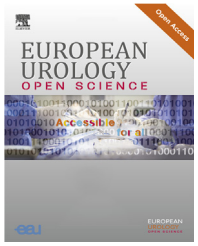

European Association of Urology

Prostate Cancer

The Mount Sinai Prebiopsy Risk Calculator for Predicting any Prostate Cancer and Clinically Significant Prostate Cancer: Development of a Risk Predictive Tool and Validation with Advanced Neural Networking, Prostate Magnetic Resonance Imaging Outcome Database, and European Randomized Study of Screening for Prostate Cancer Risk Calculator

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Article info

Article history:
Accepted April 14, 2022

Associate Editor:
Guillaume Ploussard

Abstract

Background: The European Association of Urology guidelines recommend the use of imaging, biomarkers, and risk calculators in men at risk of prostate cancer. Risk predictive calculators that combine multiparametric magnetic resonance imaging with prebiopsy variables aid as an individualized decision-making tool for patients at risk of prostate cancer, and advanced neural networking increases reliability of these tools.

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https://doi.org/10.1016/j.euros.2022.04.017

Keywords:
Prostate cancer
Biopsy
Low grade
Clinically significant
Risk calculator
Magnetic resonance imaging

Objective: To develop a comprehensive risk predictive online web-based tool using magnetic resonance imaging (MRI) and clinical data, to predict the risk of any prostate cancer (PCa) and clinically significant PCa (csPCa) applicable to biopsy-naïve men, men with a prior negative biopsy, men with prior positive low-grade cancer, and men with negative MRI.

Design, setting, and participants: Institutional review board–approved prospective data of 1902 men undergoing biopsy from October 2013 to September 2021 at Mount Sinai were collected.

Outcome measurements and statistical analysis: Univariable and multivariable analyses were used to evaluate clinical variables such as age, race, digital rectal examination, family history, prostate-specific antigen (PSA), biopsy status, Prostate Imaging Reporting and Data System score, and prostate volume, which emerged as predictors for any PCa and csPCa. Binary logistic regression was performed to study the probability. Validation was performed with advanced neural networking (ANN), multi-institutional European cohort (Prostate MRI Outcome Database [PROMOD]), and European Randomized Study of Screening for Prostate Cancer Risk Calculator (ERSPC RC) 3/4.

Results and limitations: Overall, 2363 biopsies had complete clinical information, with 57.98% any cancer and 31.40% csPCa. The prediction model was significantly associated with both any PCa and csPCa having an area under the curve (AUC) of 81.9% including clinical data. The AUC for external validation was calculated in PROMOD, ERSPC RC, and ANN for any PCa (0.82 vs 0.70 vs 0.90) and csPCa (0.82 vs 0.78 vs 0.92), respectively. This study is limited by its retrospective design and overestimation of csPCa in the PROMOD cohort.

Conclusions: The Mount Sinai Prebiopsy Risk Calculator combines PSA, imaging and clinical data to predict the risk of any PCa and csPCa for all patient settings. With accurate validation results in a large European cohort, ERSPC RC, and ANN, it exhibits its efficiency and applicability in a more generalized population. This calculator is available online in the form of a free web-based tool that can aid clinicians in better patients counseling and treatment decision-making.

Patient summary: We developed the Mount Sinai Prebiopsy Risk Calculator (MSP-RC) to assess the likelihood of any prostate cancer and clinically significant disease based on a combination of clinical and imaging characteristics. MSP-RC is applicable to all patient settings and accessible online.

1. Introduction

Prostate cancer is the most common nondermatological cancer in men, with 248 530 estimated new cases in the USA in 2021 [1]. Localized prostate cancer (PCa)-specific survival was reported to be nearly 80% with radical prostatectomy at 29 yr postoperatively in a large, landmark randomized controlled trial [2]. Thus, diagnosis at organ-confined disease is of paramount importance. The American Urological Association (AUA) PCa screening guidelines recommend shared decision-making between at-risk patients and their physicians [3]. European Association of Urology (EAU) guidelines also suggest the use of risk stratification tools for patients with a prostate-specific antigen (PSA) level below 10 ng/ml [4]. The use of multiparametric magnetic resonance imaging (mpMRI) to evaluate patients at risk for PCa and to guide targeted prostate biopsies to suspicious areas in the prostate is well supported by meta-analysis data [5]. However, mpMRI is limited by inter-reader and intercenter variability [6] and by a high rate of false negatives [7]. Moreover, a recent Cochrane meta-analysis showed that magnetic resonance imaging (MRI) has high specificity but poor and heterogeneous sensitivity for local PCa staging [8]. Therefore, mpMRI alone is insufficient as a risk stratification tool.

Risk calculators (RCs) are an attractive option as they are free and based on readily available clinical and laboratory parameters [9,10]. RCs integrate clinical data and stratify patients by incorporating PSA level, adjunct serum markers such as prostate-specific kallikrein, urine-based screening tests, clinical characteristics, and MRI findings to provide stronger predictive accuracy than any single test [6]. Many RCs have been developed using prospective multi-institution data. However, these may lack the ability to predict risk in patients with prior negative MRI [10], predict risk of low-grade cancer in biopsy-naïve patients [9], and predict clinically significant cancer in patients with prior Gleason grade (GG) 1 cancer on biopsy [10–13]. Additionally, these risk predictive models tend to be developed from multiple surgeons and institutions, which are subject to variability in biopsy techniques and inter-rater differences in interpreting mpMRI scans, both of which generate a bias [10,14,15].

Previously, these predictive risk models used linear and logistic regression, yet artificial neural networks (ANNs) have emerged as tools with stronger predictive accuracy for the detection and grading of PCa at needle biopsy [16,17]. Thus, leveraging the use of ANN in the development of risk stratification calculators may result in more accurate results in current clinical practice.

This study aims to develop a prebiopsy RC that is applicable to all patients, utilizes standard clinical parameters as predictors, and is validated via ANN, with an international cohort (Prostate MRI Outcome Database [PROMOD]) and European Randomized Study of Screening for Prostate Cancer (ERSPC)-3/4. Specifically, we develop an RC that has multidimensional functionality to predict (1) both any GG PCa and clinically significant prostate cancer (csPCa) in biopsy-naïve patients, (2) clinically significant cancer in repeat biopsies in patients with a prior biopsy positive for grade group 1 cancer, and (3) any cancer and csPCa in patients with negative MRI.

2. Patients and methods

2.1. Patient population

A retrospective analysis was performed via a prospectively maintained database on 2363 patients who underwent mpMRI followed by transrectal prostate biopsy performed by a single urologist (A.T.) between November 2013 and September 2021 at a single institution (Mount Sinai Hospital, New York City, NY, USA). All patients were consented for data collection prior to biopsy under Institutional review board protocol GCO 19-1711. Patients belonged to one of three biopsy groups: biopsy naïve (BN), previous negative biopsy (PNB), or previous positive biopsy (PPB) on active surveillance. Results of the RC were externally validated via a multi-institution database in Europe [18].

2.2. Imaging, biopsy, histopathology protocol, variables, and outcomes

All mpMRI examinations were compliant with the American College of Radiology recommendations for technical specifications [19]. All patients underwent both MRI-targeted and systematic biopsies at a single institution. A single, highly experienced genitourinary pathologist (K. H.) interpreted all biopsy specimens. For the purposes of this study, any cancer was defined as grade group 1–5 (Gleason score, 3 + 3 = 6). Clinically significant cancer was defined as grade group 2 (Gleason score, 3 + 4 = 7) or higher. The final prediction model included age, PSA, binary digital rectal examination (DRE) findings, Prostate Imaging Reporting and Data System (PI-RADS) score, and biopsy group for the purpose of analysis (see Summary in the Supplementary material).

2.3. Statistical analysis

This study included 2363 patients who underwent repeat prostate biopsy (total biopsies 2858) for a persistent clinical suspicion of PCa or as a confirmatory biopsy during active surveillance. The analysis was performed on a biopsy level, considering first-time biopsies and repeat biopsies as independent cases.

Chi-square/Fisher's exact tests were used for categorical data and Mann-Whitney *U* tests were used for continuous variables. Univariable analysis and multivariable logistic regression analyses were performed to predict the probabilities of csPCa in biopsy-naïve patients and for repeat biopsies in patients with a prior biopsy positive for grade group 1 cancer. Decision curve analysis (DCA) was used to evaluate the performance of the RC. Additionally, this model was trained and compared for efficiency using ANN (see Summary in the Supplementary material). External validation was conducted in 2248 European men using the prostate MRI outcome database (PROMOD) [18] consisting of data from five different institutions across Finland, Italy, and Sweden. The performance of the calculator was benchmarked against the previously developed ERSPC-3/4 calculator [18]. Receiver operating characteristic (ROC) plots were developed and compared between the development and validation models to demonstrate the efficacy of each model. A systematic analysis of model-derived cutoffs for "csPCa" was performed to illustrate the rates of overall biopsy saved, negative biopsy saved, and csPCa diagnosed or missed at each cutoff (Supplementary Table 1). A similar analysis and predictive model is developed for any PCa. All tests were two tailed, with $p \leq 0.05$ considered to be statistically significant. SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA), STATA version 14 (Stata Corp LLP, College Station, TX, USA), and R statistical software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

3. Results

A total of 2363 biopsies with MRI results were analyzed in the study. The study flow chart indicating inclusion and exclusion criteria is presented in Figure 1. Biopsies were grouped according to the biopsy status: BN (n = 1444), PNB (n = 514), and PPB (n = 405) on the likelihood of any PCa and on csPCa. Patient characteristics for the overall population, and stratified by biopsy group, are shown in Table 1. The median age for the Mount Sinai Prebiopsy Risk Calculator (MSP-RC) was 65.04 (interquartile range: 59.7, 70.39) and that for the PROMOD cohort was 64 (58, 69). The median prebiopsy PSA was 5.2 ng/ml, slightly lower than the validation cohort (6.5 ng/ml). The proportions of the groups were BN 61.1% (n = 1444), PNB 55.8% (n = 514), and PPB 17.1% (n = 405) in the development cohort, as compared with the proportions of 68.6%, 27.3%, and 4%, respectively, in the validation cohort (PROMOD). In the MSP-RC cohort, csPCa was detected in 34.2% (n = 742), as compared with the validation cohort where csPCa was found in 41.4% (n = 930). The proportions of PI-RADS 4 and PI-RADS 5 lesions were comparable across the training and testing cohorts, although a higher proportion of PI-RADS 1–3 lesions were noted in the MSP-RC cohort (Supplementary Table 4). In univariable analyses, age (odds ratio [OR]: 1.04; 95% confidence interval [CI]: 1.03–1.05), race (OR: 1.84; 95% CI: 1.33–2.55), PSA (OR: 1.15; 95% CI: 1.12–1.18), suspicious DRE (OR: 1.34; 95% CI: 1.12–1.60), family history (OR: 1.70; 95% CI: 1.35–2.15), MRI prostate volume (OR: 0.99; 95% CI: 0.98–0.99), MRI extracapsular extension (OR: 3.17; 95% CI: 2.18–4.61), PI-RADS score of 3 (OR: 2.84; 95% CI: 2.0–4.01) versus PI-RADS scores of 4 and 5 (OR: 9.8; 95% CI: 7.40–13.0), PNB (OR: 0.31; 95% CI: 0.23–0.40), and PPB (OR: 0.96; 95% CI: 0.76–1.20) emerged as significant predictors of csPCa with a p value of <0.0001 (Supplementary Table 2).

However on a multivariable analysis, with the inclusion of all significant variables considered in the univariable analysis, age (OR: 1.04; 95% CI: 1.03–1.06), PSA (OR: 1.18; 95% CI: 1.14–1.21), MRI volume (OR: 0.98; 95% CI: 0.98–0.99), MR PI-RADS score 3 (OR: 3.46; 95% CI: 2.39–5.00), and PI-RADS scores 4 and 5 (OR: 9.85; 95% CI: 7.32–13.25)

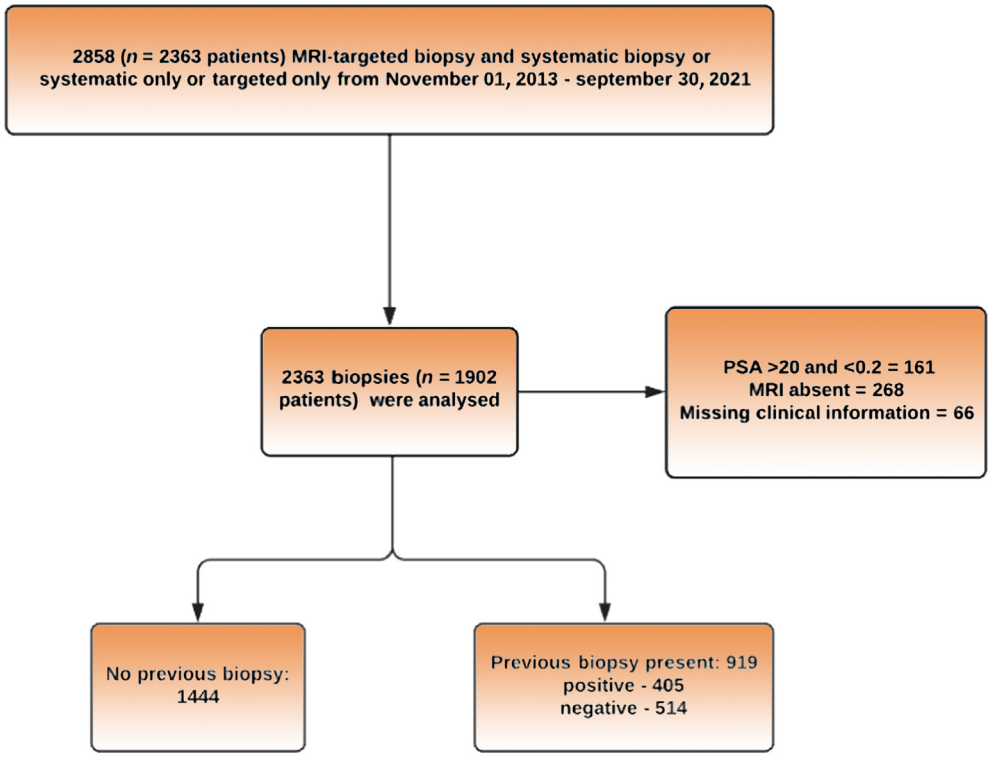


Fig. 1 – Flowchart of patient selection for study cohort, with inclusion and exclusion criteria, showing distribution of cohort into biopsy naive (no previous biopsy present) and previous biopsy present. MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Table 1 – Baseline characteristics of the study (Mount Sinai) cohort

Covariates	Overall (*n* = 2363)	Previous biopsy (*n* = 919, 38.8%)	No biopsy (*n* = 1444, 61.1%)
Age (yr)	65.04 (59.7, 70.39)	65.5 (60.19, 70.23)	65.6 (59.8,70.6)
Race, *n* (%)			
African American	157 (6.64)	55 (5.98)	102 (7.06)
Caucasian	1180 (49.94)	506 (55.06)	674 (46.68)
Hispanic Latino	31 (1.31)	13 (1.41)	18 (1.25)
Asian	72(3.05)	23 (2.50)	49 (3.39)
Unknown	161 (6.81)	53 (5.77)	108 (7.48)
Others	762 (32.25)	269 (29.27)	493 (34.14)
PSA (ng/ml)	5.17 (3.7, 7.7)	5.4 (3.5, 8.0)	5.06 (3.6, 7.5)
Family history, *n* (%)			
Negative	2013 (85.19)	808 (87.92)	1205 (83.45)
Positive	350 (14.81)	111 (12.08)	239 (16.55)
DRE, *n* (%)			
Negative	1413 (59.80)	697 (75.84)	716 (49.58)
Suspicious	950 (40.20)	222 (24.16)	728 (50.42)
MRI volume	46.00 (37.0, 65.9)	50 (38.5, 68.0)	47.1 (34.0, 68.0)
MRI highest PI-RADS, *n* (%)			
1, 2	731 (30.94)	279 (30.36)	452 (31.30)
3	416 (17.60)	165 (17.95)	251 (17.38)
4	849 (35.93)	365 (39.72)	484 (33.52)
5	367 (15.53)	110 (11.97)	257 (17.80)
Previous biopsy result, *n* (%)			
No	1444 (61.11)	NA	1444 (100)
Negative	514 (21.75)	514 (55.93)	NA
Positive	405 (17.14)	405 (44.07)	NA
Current biopsy status, *n* (%)			
Negative	993 (42.02)	387 (42.11)	606 (41.97)
Biopsy Gleason grade 1	628 (26.58)	313 (34.06)	315 (21.81)
Biopsy Gleason grade >1	742 (31.40)	219 (23.83)	523 (36.22)

DRE = digital rectal examination; MRI = magnetic resonance imaging; NA = not available; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.

Table 2 – Multivariable analysis in MSP-RC considering all preoperative variables with backward elimination method to predict any PCa (GG ≥1) and csPCa (GG ≥2)

Covariate	Multivariable model predicting any PCa (GG ≥1) AUC = 0.82			Multivariable model predicting csPCa (GG ≥2) AUC = 0.82		
	OR	95% CI	$p > \|z\|$	OR	95% CI	$p > \|z\|$
Age	1.03	1.01, 1.04	<0.001	1.04	1.03, 1.06	<0.001
Family history						
Absent*				Ref		
Present				1.84	1.40, 2.42	<0.001
DRE						
Negative*	Ref			Ref		
Suspicious	1.27	1.04, 1.56	0.020	1.13	0.92, 1.40	0.248
PSA	1.08	1.05, 1.11	<0.001	1.18	1.14, 1.21	<0.001
Biopsy setting						
Biopsy naive*				Ref		
Previous negative	0.32	0.25, 0.41	<0.001	0.27	0.20, 0.36	<0.001
Previous low-grade cancer	9.27	6.26, 13.73	<0.001	0.80	0.61, 1.04	0.101
PI-RADS						
1–2*	Ref			Ref		
3	2.27	1.72, 3.00	<0.001	3.46	2.39, 5.00	<0.001
4–5	5.44	4.34, 6.80	<0.001	9.85	7.32, 13.25	<0.001
MRI volume	0.98	0.98, 0.99	<0.001	0.98	0.98, 0.99	<0.001

AUC = area under the curve; CI = = confidence interval; csPCa = clinically significant PCa; DRE = digital rectal examination; GG = Gleason grade; MRI = magnetic resonance imaging; MSP-RC = Mount Sinai Prebiopsy Risk Calculator; OR = odds ratio; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; Ref = reference.

were statistically significant predictors of csPCa with an area under the curve (AUC) of 0.82 (Table 2). A separate predictive model was created for any PCa (Table 2). A head-to-head comparison of the conventional models by training the selected input variables via a network of hidden neurons in our three layered backpropagation ANNs yielded an 8–10% higher probability of accurately predicting csPCa. ROC plot for this ANN-predicted probabilistic network model for csPCa was 92.3%. Our model showed a higher AUC than the ERSPC for csPCa (0.81 vs 0.71). Additionally, the DeLong test showed a significant difference between the AUCs for MSP-RC, ERSPC, and ANN with a p value of <0.05 (Fig. 2).

The AUC for predicting csPCa in the external validation PROMOD cohort was similar to that in the development cohort at 0.82 (Fig. 3). DCA in this validation cohort demonstrated that the net benefit associated with the use of the model-derived probability for predicting csPCa was between ~10% and ~85%, similar to the training cohort (Fig. 4 and 5). Calibration is graphically presented in Supplementary Figure 1 (development cohort) and Supplementary Figure 2 (validation cohort). Calibration in the development cohort was optimal, while the model slightly overestimated the risk of csPCa in the external validation cohort. Results of any PCa are demonstrated in Table 2; Supplementary Tables 1 and 2; Figures 2A, 3A, 5, and 6A; and Supplementary Fig. 1.

4. Discussion

This study developed a unified RC with high predictive accuracy for csPCa (AUC = 0.82) and any PCa (AUC = 0.82). Our model demonstrates higher predictive accuracy for csPCa with ANN (AUC of 0.92). The model is readily available to patients and clinicians on the Internet at https://darasriskcalcs.shinyapps.io/MSP-RC.

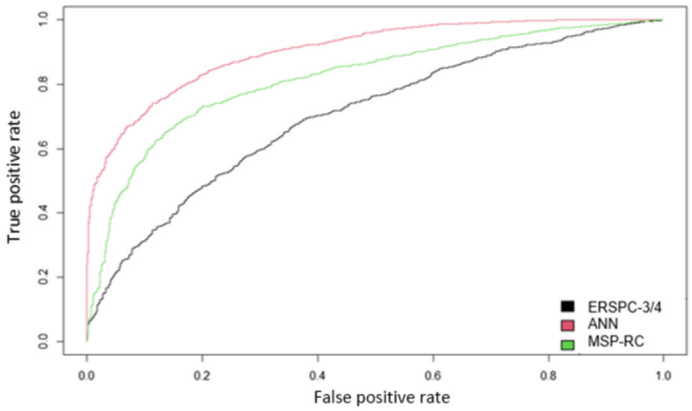
In the external validation cohort with the PROMOD database, similar accuracy to the development cohort was found, with an AUC of 82% for csPCa. Our model performs better than the ERSPC-3/4 calculator, which has an AUC of 0.78 for csPCa in the PROMOD database. These results demonstrate the reliability and generalizability of our model. It can be used to evaluate the risk for PCa on biopsy in patients with MRI PI-RADS (1–5), regardless of the number of prior prostate biopsies they have undergone or the history of previously diagnosed GG1 cancer.

Several MRI calculators and nomograms such as FPC-RC [18], Memorial Sloan Kettering Cancer Center (MSKCC) [9], Stanford [10], ModRad [12], ModDis [20], etc. described in the literature have emphasized the addition of mpMRI to other clinical parameters, confirming the strong predictive value of mpMRI in prostate biopsy decision-making. However, these studies have several limitations. Falagario et al [16,19] showed improved diagnostic accuracy when mpMRI was added to Prostate Biopsy Collaborative Group and ERSPC RCs in predicting csPCa [18]. This RC outperformed mpMRI alone for csPCa (AUC 0.80 vs 0.75). The development cohort for this study was based on a European population alone.

The original ERSPC RCs 3 and 4 have been shown in several studies to be generalizable in diverse populations and have consequently served as a benchmark for other RCs [14,15]. While demonstrating better predictive accuracy [14,15], these studies were limited by the lack of standardized MRI fusion-guided biopsies for detecting high-grade cancers, omission of MRI PI-RADS score, and applicability to only biopsy-naïve patients. A modified version of ERSPC RCs 3 and 4 [21] includes the MRI PI-RADS score, along with other clinical parameters such as age, PSA, prostate volume, and DRE, but the calculator cannot be applied to risk predic-

A

Model	AUC	De Long Test *p* value Vs ANN
ERSPC-3/4	0.7035408	<0.05
Artificial Neural Networking (ANN)	0.9035702	
MSP-RC Ca	0.8191714	<0.05



B

	AUC	De Long Test *p* value Vs ANN
ERSPC-3/4	0.7824336	<0.05
Artificial Neural Networking (ANN)	0.9225587	
MSP-RC	0.8186235	<0.05

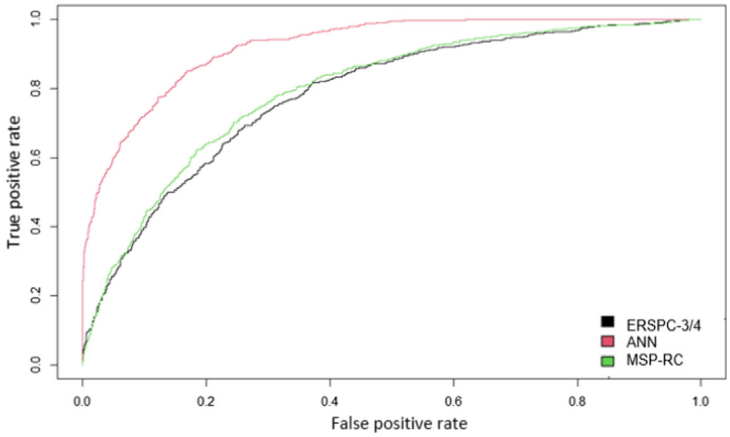


Fig. 2 – ROC plots comparing prediction AUC of MSP-RC, ERSPC-RC, and ANN for (A) any PCa (0.82 vs 0.70 vs 0.90) and (B) csPCa (0.82 vs 0.78 vs 0.92). Black line represents ERSPC- 3/4, red line represents ANN, and green line represents MSP-RC. ANN = advanced neural networking; AUC = area under the curve; csPCa = clinically significant PCa; ERSPC = European Randomized Study of Screening for Prostate Cancer; MSP-RC = Mount Sinai Prebiopsy Risk Calculator; PCa = prostate cancer.

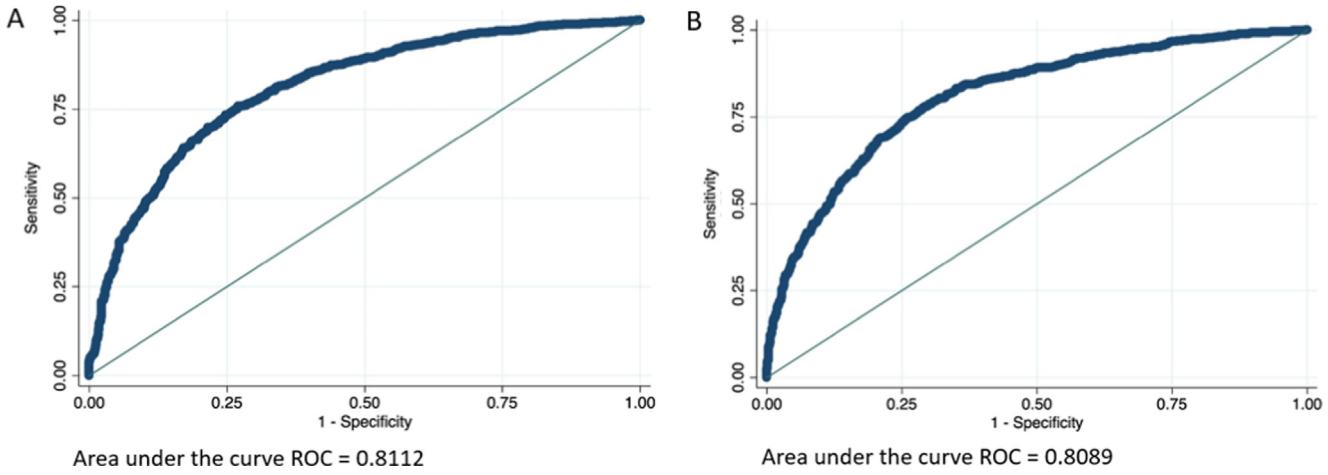


Fig. 3 – ROC plots comparing prediction AUC of external validation in PROMOD for (A) any PCa (0.82) and (B) csPCa (0.82) in the validation cohort. AUC = area under the curve; csPCa = clinically significant PCa; MRI = magnetic resonance imaging; PCa = prostate cancer; PROMOD = Prostate MRI Outcome Database; ROC = receiver operating characteristics.

tion for clinically significant cancer in patients with a previous GG1 who are on active surveillance. Moreover, the basis for the development of the ERSPC RC was European white men (as opposed to a more diverse population at risk for PCa), and the use of biparametric MRI and that of the outdated PI-RADS version 1 protocol are notable limitations.

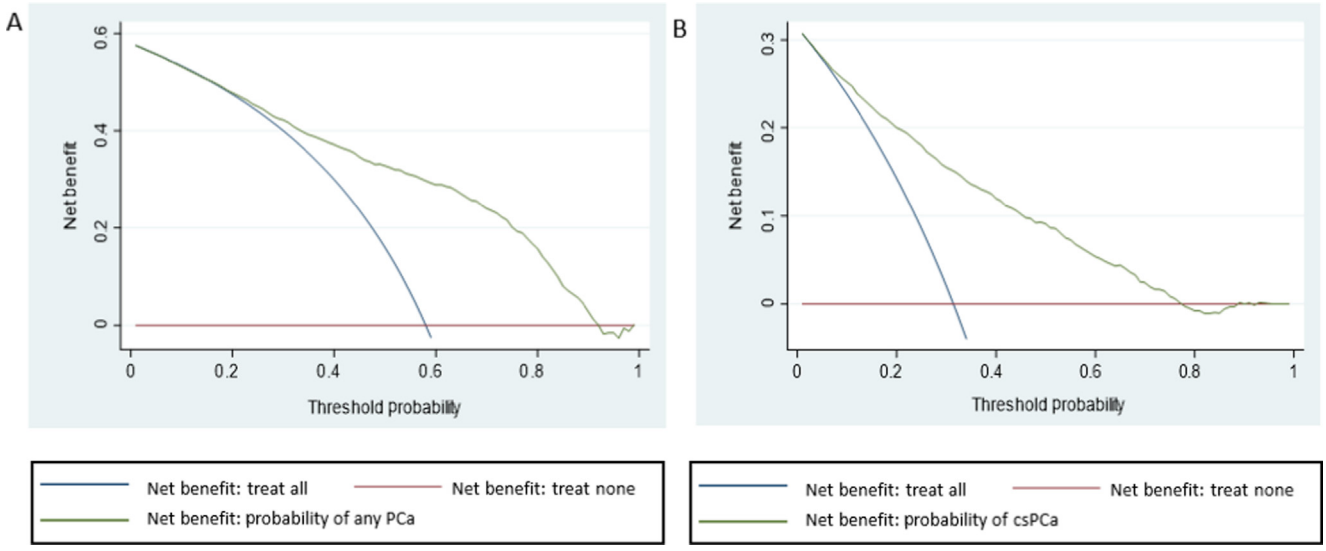


Fig. 4 – Decision curve analysis of (A) any PCa and (B) csPCa MSH model in the MSP-RC cohort. Red line: assume that no patients have undergone biopsy; blue line: assume that all patients undergone performed biopsy; and green line: prediction model. csPCa = clinically significant PCa; MSP-RC = Mount Sinai Prebiopsy Risk Calculator; PCa = prostate cancer.

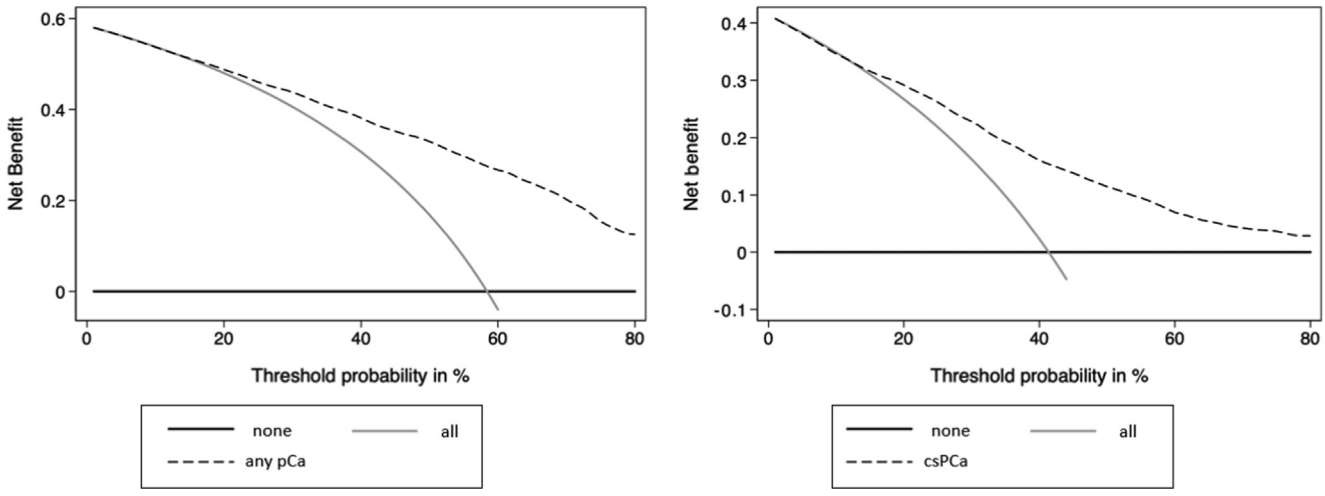


Fig. 5 – Decision curve analysis of (A) any PCa and (B) csPCa MSP-RC model in the external validation (PROMOD) cohort. Blue line: assume that no patients have undergone biopsy; grey line: assume that all patients have undergone biopsy; and dashed line: prediction model. csPCa = clinically significant PCa; MRI = magnetic resonance imaging; MSP-RC = Mount Sinai Prebiopsy Risk Calculator; PCa = prostate cancer; PROMOD = Prostate MRI Outcome Database.

A recent study by Lee et al[22] comparing the current six most efficient RCs showed the RC by van Leeuwen et al. [23] to have the greatest effectiveness (AUC 86%), missing only 4% of csPCa at 15% threshold in an Asian cohort. However, similar to many of the abovementioned tools, nonaccessibility (ie, it is not an online web-based tool) limits its clinical utility.

The contemporary prostate biopsy risk calculator (MSKCC) is based on multiple heterogeneous cohorts, outperformed the leading North American risk tool (Prostate Cancer Prevention Trial RC) in predicting the risk of high-grade PCa with external validation in a European cohort, but does not consider MRI PI-RADS scores and does not include the prediction of low-grade cancer [9]. Additionally, Wang et al [10] demonstrated the efficacy of a nomogram combining mpMRI with other clinical variables such as age, race, PSA, etc. This group developed a model that showed an AUC of 0.78 for csPCa, which exhibited generalizability limited to a North American patient population and not applicable to patients with negative MRI, and does not predict the risk of low-grade PCa. More recently, a nomogram for risk prediction in patients with negative MRI findings developed by Wagaskar et al.[24] demonstrated saving 8% csPCa cases that would have been missed without a biopsy based on negative MRI findings. However, there are some subsets of patients who even with a PI-RADS 4 have a low risk of having csPCa. This is especially true in the setting of patients with a previous negative biopsy with low PSA val-

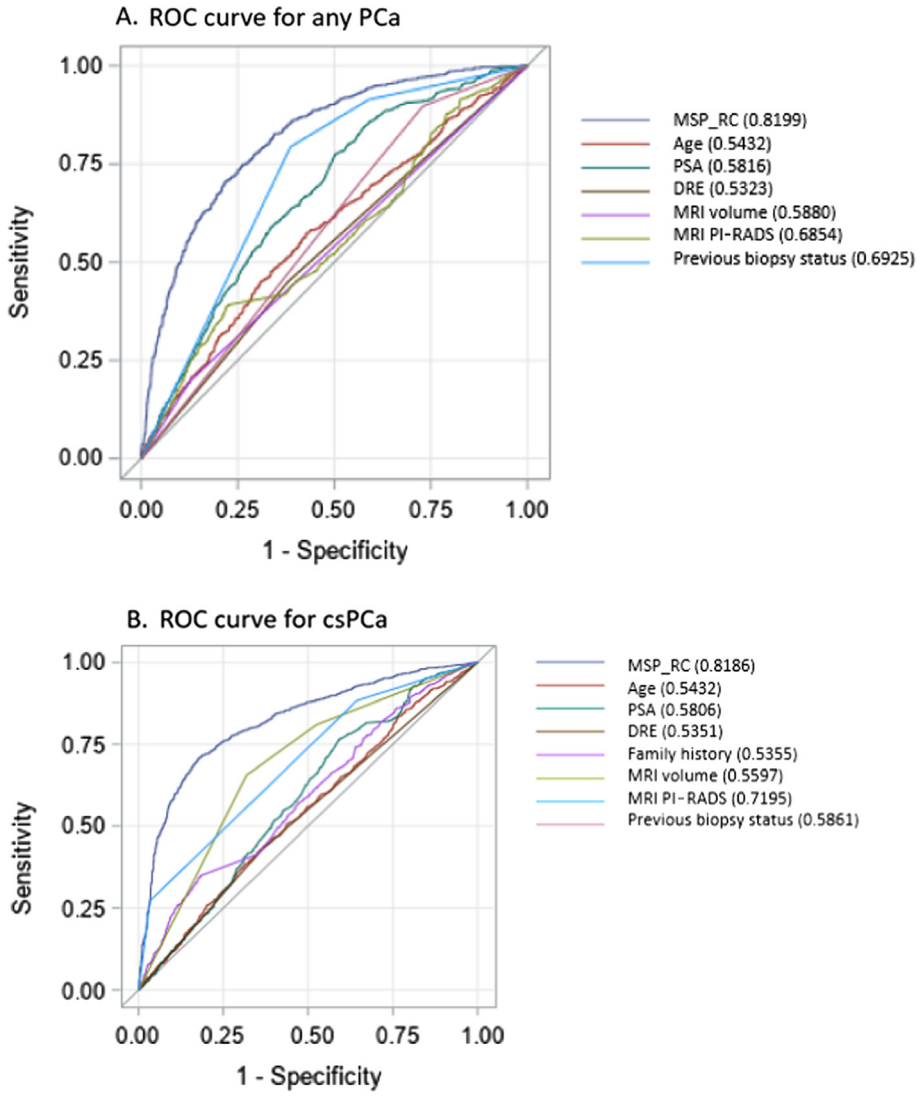


Fig. 6 – ROC plots comparing prediction AUC for (A) any PCa and (B) csPCa in the training (Mount Sinai) cohort. AUC = area under the curve; csPCa = clinically significant PCa; DRE = digital rectal examination; PI-RADS = Prostate Imaging Reporting and Data System; PCa = = prostate cancer; ROC = receiver operating characteristics.

ues. Additionally, our model may be helpful for counseling patients about their MRI results in a more individualized approach. Conversely, some patients with negative MRI may consider biopsy as well based on the other clinical parameters. We believe that the model developed in a population with patients with negative MRI could be of limited utility.

Previously developed RCs and nomograms integrate biopsy data from multiple surgeons, are externally validated to a patient population in a single region, exclude prediction of cancer in patients with negative MRI, are not available online, or predict only clinically significant cancer in biopsy-naïve patients or patients with a previous negative biopsy. Other groups have used different mpMRI scoring systems such as the Likert scale and mpMRI suspicion scores. These factors limit the comprehensiveness of these models and their accessibility for decision-making and clinical application globally in diverse patient settings. Additionally, these abovementioned conventional regression models and calculators lack testing in an artificial intelligence–based neural networking tool. Several studies in the past have demonstrated ANN-based models to have higher accuracy, sensitivity, specificity, negative predictive value, and positive predictive value than individual biomarkers and logistic regression models based on the combination of clinical parameters for prebiopsy decision-making [25–27]. In addition, studies show ANN to have improved diagnostic power as compared with the conventional logistic regression models [17,28,29], but there is a need for an ANN-tested tool that includes standard parameters such as MRI PI-RADS score, prostate volume, and family history, and is easily accessible online. Thus, to overcome the biases in the existing clinical models, calculators, and nomograms, we created a comprehensive risk predictive model that performed well across multiple international institutions, provided better prediction with advanced neural networking, and provided better results than any formal RC. Our ANN-tested model incorporates all relevant clinical information, including age, family history, MRI prostate volume, MRI PI-RADS score or prior negative MRI status, family

history of PCa, and previous biopsy status, with online accessibility that overcomes the limitations of existing RCs.

The improved results of our model compared with the artificial intelligence–based ANN system, its verification with an external validation cohort, and its web-based accessibility as a formal RC make it unique and applicable to a wide population with differences across ethnicities, disease prevalence, and variations in clinical practices.

This study has a number of limitations. It is a retrospective study that contains an inherent bias. The MRI technical specifications for PI-RADS version 1 were used for some of the MRI scans. In addition, this study includes exclusively transrectal biopsies, although transperineal fusion biopsies are known to provide more accurate detection rates for PCa [30,31]. Nevertheless, our RC is well suited for routine clinical use, as transrectal RCs are more clinically common than transperineal ones [32].

5. Conclusions

We developed and externally validated the MSP-RC to assess the likelihood of any PCa and csPCa based on a combination of clinical and imaging characteristics. This comprehensive model ANN-tested web-based tool will assist urologists in real-time patient counseling and clinical decision-making.

***Author contributions*:** Ash Tewari 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.

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Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Tewari.
Other: None.

Financial disclosures: Ash Tewari certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Ash Tewari has served as a site PI on pharma/industry-sponsored clinical trials from Kite Pharma Inc., Lumicell, Inc., Dendron Pharmaceuticals, LLC, Oncovir Inc., Blue Earth Diagnostics Ltd., RhoVac ApS., Bayer HealthCare Pharmaceuticals Inc., and Janssen Research and Development, LLC; has received research funding (grants) to his institution from DOD, NIH, Axogen, Intuitive Surgical, AMBF, and other philanthropy; has served as an unpaid consultant to Roivant Biosciences and advisor to Promaxo; and owns equity in Promaxo. Zach Dovey is a Medical Director and stock owner by shares in MediTech Holdings Ltd.

***Funding/Support and role of the sponsor*:** None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.04.017.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
[2] Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in prostate cancer—29-year follow-up. N Engl J Med 2018;379:2319–29.
[3] Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. J Urol 2013;190:419–26.
[4] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.
[5] Elwenspoek MMC, Sheppard AL, McInnes MDF, et al. Comparison of multiparametric magnetic resonance imaging and targeted biopsy with systematic biopsy alone for the diagnosis of prostate cancer. JAMA Netw Open 2019;2:e198427.
[6] Wajswol E, Winoker JS, Anastos H, et al. A cohort of transperineal electromagnetically tracked magnetic resonance imaging/ultrasonography fusion-guided biopsy: assessing the impact of inter-reader variability on cancer detection. BJU Int 2020;125:531–40.
[7] Borofsky S, George AK, Gaur S, et al. What are we missing? False-negative cancers at multiparametric MR imaging of the prostate. Radiology 2018;286:186–95.
[8] Drost FJ, Osses DF, Nieboer D, et al. Prostate MRI, with or without targeted biopsy and standard biopsy for detecting prostate cancer: a Cochrane systematic review and meta-analysis. Eur Urol Suppl 2019;18:e728–9.
[9] Ankerst DP, Straubinger J, Selig K, et al. A contemporary prostate biopsy risk calculator based on multiple heterogeneous cohorts. Eur Urol 2018;74:197–203.
[10] Wang NN, Zhou SR, Chen L, et al. The Stanford prostate cancer calculator: development and external validation of online nomograms incorporating PIRADS scores to predict clinically significant prostate cancer. Urol Oncol 2021;39:831.e19–27.
[11] Radtke JP, Wiesenfarth M, Kesch C, et al. Combined clinical parameters and multiparametric magnetic resonance imaging for advanced risk modeling of prostate cancer—patient-tailored risk stratification can reduce unnecessary biopsies. Eur Urol 2017;72:888–96.
[12] Radtke JP, Giganti F, Wiesenfarth M, et al. Prediction of significant prostate cancer in biopsy-naïve men: validation of a novel risk model combining MRI and clinical parameters and comparison to an ERSPC risk calculator and PI-RADS. PLoS One 2019;14:e0221350.
[13] Mehralivand S, Shih JH, Rais-Bahrami S, et al. A magnetic resonance imaging–based prediction model for prostate biopsy risk stratification. JAMA Oncol 2018;4:678–85.
[14] Gayet M, Mannaerts CK, Nieboer D, et al. Prediction of prostate cancer: external validation of the ERSPC risk calculator in a contemporary Dutch clinical cohort. Eur Urol Focus 2018;4:228–34.
[15] Jalali A, Foley RW, Maweni RM, et al. A risk calculator to inform the need for a prostate biopsy: a rapid access clinic cohort. BMC Med Inform Decis Mak 2020;20:148.
[16] Falagario UG, Silecchia G, Bruno SM, et al. Does multiparametric magnetic resonance of prostate outperform risk calculators in predicting prostate cancer in biopsy naïve patients? Front Oncol 2020;10:603384.

[17] Eberhardt SC. Local staging of prostate cancer with MRI: a need for standardization. Radiology 2019;290:720–1.
[18] Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System version 2.1: 2019 update of Prostate Imaging Reporting and Data System version 2. Eur Urol 2019;76:340–51.
[19] Falagario UG, Jambor I, Lantz A, et al. Combined use of prostate-specific antigen density and magnetic resonance imaging for prostate biopsy decision planning: a retrospective multi-institutional study using the Prostate Magnetic Resonance Imaging Outcome Database (PROMOD). Eur Urol Oncol 2021;4:971–9.
[20] Distler FA, Radtke JP, Bonekamp D, et al. The value of PSA density in combination with PI-RADS™ for the accuracy of prostate cancer prediction. J Urol 2017;198:575–82.
[21] Alberts AR, Roobol MJ, Verbeek JFM, et al. Prediction of high-grade prostate cancer following multiparametric magnetic resonance imaging: improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculators. Eur Urol 2019;75:310–8.
[22] Lee HJ, Lee A, Yang XY, et al. External validation and comparison of magnetic resonance imaging-based predictive models for clinically significant prostate cancer. Urol Oncol 2021;39:783.e1–783.e10.
[23] van Leeuwen PJ, Hayen A, Thompson JE, et al. A multiparametric magnetic resonance imaging-based risk model to determine the risk of significant prostate cancer prior to biopsy. BJU Int 2017;120:774–81.
[24] Wagaskar VG, Levy M, Ratnani P, et al. Clinical utility of negative multiparametric magnetic resonance imaging in the diagnosis of prostate cancer and clinically significant prostate cancer. Eur Urol Open Sci 2021;28:9–16.
[25] Meyer AR, Mamawala M, Winoker JS, et al. Transperineal prostate biopsy improves the detection of clinically significant prostate cancer among men on active surveillance. J Urol 2021;205:1069–74.
[26] Pepe P, Garufi A, Priolo G, Pennisi M. Transperineal versus transrectal MRI/TRUS fusion targeted biopsy: detection rate of clinically significant prostate cancer. Clin Genitourin Cancer 2017;15:e33–6.
[27] Roberts MJ, Bennett HY, Harris PN, et al. Prostate biopsy-related infection: a systematic review of risk factors, prevention strategies, and management approaches. Urology 2017;104:11–21.
[28] Babaian RJ, Fritsche H, Ayala A, et al. Performance of a neural network in detecting prostate cancer in the prostate-specific antigen reflex range of 2.5 to 4.0 ng/mL. Urology 2000;56:1000–6.
[29] Stephan C, Jung K, Cammann H, et al. An artificial neural network considerably improves the diagnostic power of percent free prostate-specific antigen in prostate cancer diagnosis: results of a 5-year investigation. Int J Cancer 2002;99:466–73.
[30] Twilt JJ, van Leeuwen KG, Huisman HJ, Fütterer JJ, de Rooij M. Artificial intelligence based algorithms for prostate cancer classification and detection on magnetic resonance imaging: a narrative review. Diagnostics 2021;11:959.
[31] Djavan B, Remzi M, Zlotta A, Seitz C, Snow P, Marberger M. Novel artificial neural network for early detection of prostate cancer. J Clin Oncol 2002;20:921–9.
[32] Takeuchi T, Hattori-Kato M, Okuno Y, Iwai S, Mikami K. Prediction of prostate cancer by deep learning with multilayer artificial neural network. Can Urol Assoc J 2019;13:E145–50.