Integration of magnetic resonance imaging into prostate cancer nomograms

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Abstract: The decision whether to undergo prostate biopsy must be carefully weighed. Nomograms have widely been utilized as risk calculators to improve the identification of prostate cancer by weighing several clinical factors. The recent inclusion of multiparametric magnetic resonance imaging (mpMRI) findings into nomograms has drastically improved their nomogram's accuracy at identifying clinically significant prostate cancer. Several novel nomograms have incorporated mpMRI to aid in the decision-making process in proceeding with a prostate biopsy in patients who are biopsy-naïve, have a prior negative biopsy, or are on active surveillance. Furthermore, novel nomograms have incorporated mpMRI to aid in treatment planning of definitive therapy. This literature review highlights how the inclusion of mpMRI into prostate cancer nomograms has improved upon their performance, potentially reduce unnecessary procedures, and enhance the individual risk assessment by improving confidence in clinical decision-making by both patients and their care providers.

Keywords: multiparametric magnetic resonance imaging, nomogram, prostatic adenocarcinoma, screening

Introduction

Prostate cancer accounts for 26% of all cancer diagnoses and is the second leading cause of cancer-related deaths in American men.[1] Prostate-specific antigen (PSA) screening prior to prostate biopsy in the European Randomized Study for Screening for Prostate Cancer (ERSPC) showed a decrease in death from prostate cancer by 31%. However, the use of PSA alone as a screening tool for clinically significant (Grade Group 2 or higher) prostate cancer is controversial, given its low specificity and low positive predictive value for the detection of clinically significant prostate cancer.[2,3] Prostate biopsy is an invasive diagnostic procedure with well-recognized risks including hematuria, urinary tract infections, anal bleeding, and sepsis. After undergoing biopsy, 60–70% of patient's initial systematic prostate biopsy results are negative due to the very limited and random sampling approach associated with the standard-of-care method.[4] In addition, unnecessary prostate biopsy sessions have led to the over diagnosis of low-risk prostate cancer, which places an undue psychologic burden on patients and potential

unnecessary treatments.[5] Alternatively, overtreatment of low-grade, biologically indolent prostate cancer puts patients at excessive risk for treatment-related side effects and potential complications. Therefore, there has been a strong incentive to better select men for prostate biopsy beyond the initial PSA elevation trigger.[6,7]

Magnetic resonance imaging (MRI) has been used for the assessment of the prostate gland since the 1980s but was largely utilized to define locoregional staging.[6] In 2012, the European Society of Urogenital Radiology published guidelines for the Prostate Imaging-Reporting and Data System (PI-RADS), the standardized scoring system for prostate cancer, and has now undergone multiple version updates.[8,9] Multiparametric magnetic resonance imaging (mpMRI) combines at least two functional imaging modalities that also include diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC) derived from DWI sequences, and dynamic contrast enhancement to assess prostate tissue for the potential presence of malignant

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transformation. Several studies have demonstrated the high level of accuracy of mpMRI in the diagnosis of prostate cancer.[10–13] The prostate MR imaging study (PROMIS) validated mpMRI accuracy in a multicenter, paired-cohort study with 576 men who underwent mpMRI followed by transrectal ultrasound (TRUS) and a systematic template biopsy schema. mpMRI was more sensitive in detecting clinically significant prostate cancer than TRUS systematic biopsy alone (93% *vs* 48%, $p < 0.0001$).[14] Of note, mpMRI alone in detecting clinically significant prostate cancer has a recognized false-negative rate. Borofsky *et al.*[15] concluded that mpMRI has a 99% true-positive rate of clinically significant prostate cancer localization, but a clinically important tumor was missed in 26% of patients.

Decision-making models are commonly utilized in the management of prostate cancer. Nomograms are the most frequently utilized and allow clinicians to integrate patient data into risk and prognostic assessments to aid in clinical decision-making. Classically, nomograms have been a two-dimensional graphical device but now are generally an electronic formula on a device that inputs specific variables to provide the likelihood of the endpoint. Development of nomograms is a multi-step process that begins with the selection of a clinical question and identifying variables of potential interest. As there are an infinite number of possible variables to include in a nomogram, variables are generally derived based on established associations that have previously been postulated or proven to be clinically relevant. Once the model is established, it is validated internally to determine whether the model can usefully discriminate the outcome of interest, which is usually expressed as an area under the curve (AUC) on a receiver operating characteristic curve (ROC). Once the accuracy of the nomogram is established, thresholds for clinical decision-making can then be derived through decision-curve analyses. Finally, models should be externally validated with a population different from the testing population to confirm generalizability for wider adoption and application in clinical practices beyond the subpopulation from which the risk calculator was developed.

In this literature review, we examine how clinical decision-making models have been enhanced over time by the inclusion of mpMRI and their clinical impact on improving the diagnosis of clinically significant prostate cancer. In addition, we will review the role of nomograms on enhancing treatment plans in men diagnosed with clinically localized prostate cancer.

Nomograms in prostate cancer screening

Initial prostate biopsy nomograms were based on a study in 1994 that paired digital rectal exam (DRE) findings with serum PSA concentrations. Of the 160 volunteers who underwent radical prostatectomy (RP) and pathological staging, identification of organ-confined prostate cancer was identified in 71% of patients using PSA alone, but DRE was only able to identify 56%. This study demonstrated that combining PSA and DRE findings led to the improved identification of organ-confined disease in 78% of patients. Ultimately, the study concluded that prostate biopsy should be considered if either the PSA level is greater than 4 ng/mL or digital rectal examination is suspicious for cancer, even in the absence of abnormal TRUS findings.[16,17]

Studies prior to mpMRI

Early, large-scale prostate cancer screening studies used 4.0 ng/mL as the threshold for recommendation for prostate cancer biopsy; however, it was noted that men with PSA levels between 2.5 and 4.0 ng/mL had similar rates of prostate cancer.[18,19] This prompted the need to find additional factors to help predict prostate cancer. In 1999, Eastham *et al.* developed a nomogram that predicted the probability of positive prostate biopsy in men with an abnormal DRE exam and elevated PSA. In the study, the group noted that while PSA alone would be easier for patients, a nomogram utilizing multiple factors could provide a better percentage for detecting prostate cancer and better guide the decision-making process. In their analysis of pre-biopsy risk factors (age, race, and serum PSA), only serum PSA was an independent predictor of a positive prostate biopsy.[20] This nomogram was later upgraded to also include percent-free PSA, family history, and DRE findings. This new model was found to have an AUC of 0.71.[21] A similar model to the updated model was created in 2007, known as the Sunnybrook nomogram, named after the patients who were referred to the Sunnybrook Health Sciences Center and University Health Network in Toronto, Canada.[22]

Finne *et al.* utilized artificial neural networking to create a multilayer perception and logical

regression for prostate cancer screening to eliminate false-positive PSA findings. The enhanced model included the proportion of free PSA along with DRE results, and prostate volume for men with total serum PSA concentrations ranging from 4 to 10 ng/mL. The study was successful in creating a model with a sensitivity of 95% that eliminated 19% of the false-positive PSA results.[23] This was then validated in a multi-center study that grouped patients into 2–4 and 4–10 ng/mL, with specificities of 90% and 62%, respectively.[24] However, this model has not been well utilized, as it was not easily accessible for physicians to use.

In 2003, Garzotto *et al.* expanded the PSA and DRE nomogram to include age >75 and TRUS findings as independent predictors in a single institution study. The inclusion of hypoechoic TRUS findings increased the AUC to 0.73 from 0.62 in this population. The study suggested that this model could reduce unnecessary biopsy procedures by 24%.[25] TRUS imaging initially showed promise in improving clinical decision-making, but the PROMIS study highlighted the inability for TRUS-guided biopsy to identify true clinically significant prostate cancer with sensitivities of 93% for mpMRI and 48% for TRUS-guided biopsy.[14] Although, in the study, mpMRI performed poorer in ruling out clinically significant prostate cancer having specificities of 41% for mpMRI and 96% for TRUS-biopsy.

This may be due to the suggested poor ability to identify cribiform morphology Gleason pattern 4 on mpMRI.[26] Although, it has been recently shown that cribiform morphology could accurately be identified in the peripheral zone by primarily focusing upon ADC values from the DWI of the mpMRI.[27] This study highlighted the need for information in addition to mpMRI in order to determine those that should and should not be biopsied. The nomograms presented below highlight the AUC of each nomogram without specifically highlighting sensitivity or specificity as these values change with different cut-off thresholds for detection of clinically significant prostate cancers. Further work may be necessary to identify if widely accepted cut-off thresholds or individual nomogram cut-offs should be utilized to maximize utility and comparability (Table 1).

Table 1. mpMRI nomograms for prostate cancer for patients that are biopsy naïve, have had previous biopsies, on active surveillance and for treatment planning.

Category	Study	Population (study size)	Risk factors	Outcome	Accuracy: AUC	External validation AUC
Biopsy Naïve						
	Distler *et al.*[28]	Germany (1040)	PSA density and PIRADS v1.0	GG ⩾ 2	0.79	0.83[29]
	Radtke *et al.*[30]	Germany (1159)	TRUS lesions (focal hypoechoic lesions), DRE, TRUS-measured prostate volume, PSA, and PIRADS v1.0	GG ⩾ 2	0.84	0.85[29]
	Pullen *et al.*[29]	Germany (307)	TRUS lesions (focal hypoechoic lesions), DRE, TRUS-measured prostate volume, PSA, and PIRADS v2.0	GG ⩾ 2	0.82	No
	Fenstermaker *et al.*[31]	New York, USA (187)	PCA3 and MRI suspicion score	Cancer detection on MRI fusion-targeted biopsy	0.83	No
Previous Negative Biopsy						
	Radtke *et al.*[30]	Germany (1,159)	TRUS lesions (focal hypoechoic lesions), DRE, TRUS-measured prostate volume, PSA, previous biopsy, and PIRADS v1.0	GG ⩾ 2	0.78	No

(Continued)

Table 1. (Continued)

Category	Study	Population (study size)	Risk factors	Outcome	Accuracy: AUC	External validation AUC
	van Leeuwen et al.[32]	Australia (393)	PSA level, DRE, prostate volume, previous biopsy, and PIRADS v1.0	Gleason 7 with >5% grade 4, ≥20% cores positive or ≥7 mm of cancer in any core	0.88	No
	Truong et al.[33]	New York, Alabama, USA (285)	Age, PSA, prostate, volume, and PIRADS	Benign pathology on both MRI/US fusion biopsy and systematic biopsy	0.825	0.79[34]
	Alberts et al.[35]	Michigan, USA (1225)	TRUS lesions (focal hypoechoic lesions), DRE, TRUS-measured prostate volume, PSA, previous biopsy, mpMRI, and age	GG ≥ 2	0.85	No
	Wagaskar et al.[36]	New York, USA (574)	mpMRI, 4Kscore, PIRADS ≥ 4, and a prior negative biopsy	GG ≥ 2	0.88	No
	Wang et al.[37]	California, USA (810)	Biopsy history, PSA density, PIRADS score of 4 or 5, Caucasian race, and age	GG ≥ 2	0.78	0.85 (Connecticut, USA), 0.80 (Alabama, USA)[37]
	Patel et al.[38]	Illinois, USA (900)	PSA, PSA density, prostate volume, and PIRADS score	GG ≥ 2	0.877	No
Active Surveillance						
	Lai et al.[39]	Alabama, USA (76)	PSA density, duration between diagnosis and MRI/US fusion biopsies, PIRADS, and total lesion density	Patients on AS upgrading from GG1	0.84	No
	Lantz et al.[40]	New York, USA (1284)	Age at surgery, PSA, GG, MRI prostate volume, PIRADS, and MRI extraprostatic extension	Non-organ–confined disease and/or lymph node invasion and/or GG ≥ 3 at RP	0.71	No
	Luzzago et al.[41]	Italy (1837)	PSA density, GG, PIRADS score, and MRI extraprostatic extension	GG ≥ 3 3 and/or pathological T-stage (pT) ≥3a and/or pathological N stage (pN) 1.	0.84	No
Treatment Planning						
	Soeterik et al.[42]	Netherlands (1062)	mpMRI T-stage, and MSKCC[43]	Lymph node invasion	0.72	No
	Soeterik et al.[42]	Netherlands (1062)	mpMRI T-stage and Briganti et al.[44]	Lymph node invasion	0.75	No
	Gandaglia et al.[45]	Five European Tertiary Referral Centers (479)	PSA, clinical stage detected by mpMRI, GG, lesion diameter according to mpMRI, and percentage of core with clinically significant prostate cancer at systematic biopsy	Lymph node invasion	0.86	No
	Martini et al.[46]	New York (829)	PSA level, clinical stage, biopsy findings, and mpMRI	Extracapsular extension	0.8211	No

(Continued)

Table 1. (Continued)

Category	Study	Population (study size)	Risk factors	Outcome	Accuracy: AUC	External validation AUC
	Rayn *et al.*[47]	Maryland, USA (532)	MSKCC[43] and mpMRI	Organ confined disease Extraprostate extension Seminal vesicle invasion Lymph node involvement	0.90 0.80 0.90 0.88	No
	Gandaglia *et al.*[48]	Five European Centers (614)	PSA, clinical stage at DRE, GG at MRI-targeted biopsy, and mpMRI	Extracapsular extension Seminal vesicle invasion ISUP group upgrading at final pathology	0.73 0.81 0.73	0.718[49] 0.685[49] No
	Soeterik *et al.*[50]	Netherlands (887)	PSA density, DRE staging, mpMRI staging, ISUP grades 3–5, and percentage of positive cores	Extraprostatic extension	0.82	0.83, 0.78[50]

AS, active surveillance; AUC, area under the curve; DRE, digital rectal exam; GG, grade group; ISUP, International Society of Urological Pathology; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; MSKCC, Memorial Sloan Kettering Cancer Center; PIRADS, Prostate Imaging-Reporting and Data Systems; PSA, prostate-specific antigen; RP, radical prostatectomy; TRUS, transrectal ultrasound; US, ultrasound.
The table includes the study that it was published in, the patient location and number in the study used to create the nomogram, the risk factors used in the nomogram, outcomes for the nomogram, internal validation AUC and external validation AUC with corresponding study.

MpMRI nomograms

Biopsy naive. The ERSPC was used in creating an initial circular sliding nomogram utilizing PSA, prostate volume, DRE, and TRUS findings but later evolved to include seven different risk calculators for the stages of treatment for prostate cancer.[51] For example, Step 3, biopsy-naive, of the ERSPC risk calculator (ERSPC-RC3) used PSA, DRE, TRUS prostate volume, and TRUS imaging abnormality to determine whether patients should be biopsied.[52] This study and other validation studies suggested that this model could reduce unnecessary biopsy by 20–33%.[53–59] Gayet *et al.* externally validated ERSPC-RC3 in a cohort of a Dutch population which had an AUC of 0.78 and 0.90 for any prostate cancer and significant prostate cancer. In addition to European validations of the ERSPC, external validation has been performed in Asian populations. The epidemiology in Asia is vastly different having a 25-fold decrease in prostate cancer incidence.[60] In China, a separate nomogram was designed to identify a Gleason score of ≥7 using PSA, free PSA or PSA density, DRE texture, DRE nodules, and B-ultrasound results. In this study, the AUC for PSA, free PSA and PSA density in predicting Gleason score ≥7 was 0.831 in the new model.[61]

The first risk calculators to utilize mpMRI for the identification of clinically significant prostate cancer

were created in 2017.[28,30,32] ModDis, a nomogram created by Distler *et al.*, studied 1040 biopsy-naive men in Germany and found combining PSA density and PI-RADS scoring improved the negative predictive value when compared to PI-RADS suspicion alone. This study had an AUC of 0.79, compared to 0.75 with PI-RADS suspicion alone. Concurrently, ModRad, created by Radtke *et al.*[30] from 1159 German biopsy-naive men, utilized the ERSPC-RC3 as described above but added in PI-RADSv1.0 scoring. PSA, prostate volume, digital rectal examination, and PI-RADS scoring were all significant predictors of clinically significant prostate cancer. The Radtke *et al.*[30] study highlighted the improvement in NPV in nomograms as compared to mpMRI alone; for example, the NPV at a 20% probability of significant prostate cancer cut-off improved from 0.73 to 0.77 when comparing their nomogram to mpMRI alone. A study later by Pullen *et al.* externally validated these models in a group of 307 German men and compared them to ERSPC with PI-RADSv2.0. The AUC for the risk model ERSPC with PI-RADSv2.0, ModDis, and ModRad, were found to be 0.83, 0.85, and 0.82, respectively. The incorporation of mpMRI into these nomograms improved their AUC when compared to the AUC of ERSPC-RC3 alone and PI-RADS alone (0.81 and 0.76, respectively).[28,30,29]

Although mpMRI increased the AUC for predicting clinically significant prostate cancer, it can

also lead to excessive resource utilization and costs. That is where Troung *et al.* utilized machine learning to help identify those that should undergo mpMRI for both biopsy-naive and prior negative biopsy patients. This multi-institution study of 1269 patients at Birmingham, Rochester, Chicago, and Houston was named BiRCH. The machine-learning model used age, PSA, and prostate volume for their logistical regression model for predicting PIRADS of 4 or 5. The model's AUC was 0.73 on internal validation ($n = 811$) and 0.74 and 0.744 on external validation at two separate institutions ($n = 88$ and $n = 126$).[62]

In 2013, Hansen *et al.* added PCA3 mRNA levels to their nomogram to determine whether to perform an initial prostate biopsy. Applying the models for the prediction of high-grade prostate cancer and a PCA3-based model with a cut-off score of 21 gave an AUC of 0.829.[63] This nomogram was later updated to include race and family history. The new nomogram was found to have a concordance index of 0.768 for those diagnosed with high-grade prostate cancer in their cohort of 1620 men.[64] However, a study by Fenstermaker *et al.* found that the addition of PCA3 offered little benefit for predicting detection of prostate cancer over mpMRI alone. This study of 187 men in New York intended to combine PCA3 with MRI suspicion score (mSS). mSS alone had a significantly higher AUC for prostate cancer than PCA3 alone (0.815 *vs* 0.690, $p = .0013$). The addition of PCA3 to mSS only slightly increased the AUC from 0.831 *versus* 0.793 for mSS alone, $p = 0.0434$.[31]

Previous negative biopsy. The Prostate Cancer Prevention trial (PCPT) identified PSA, family history, abnormal DRE, and prior negative biopsy as useful predictive factors for any prostate cancer. However, PSA, abnormal DRE, older age at biopsy, previous negative biopsy, and African-American (AA) race were factors in predicting higher-grade disease (Gleason score $\geqslant 7$). The PCPT Risk Calculator (PCPTRC) has been updated several times over the years. In 2013, a risk calculator based on PCPT was created that now included prostate volume and AUA symptom score.[65] The official PCPTRC was updated first in 2014 to include low-risk prostate cancer, and then again in 2018.[66–68] The 2014 PCPT risk calculator was externally validated by the Prostate Biopsy Collaborative Group (PCGB) consisting of 25,449 biopsies from 10 international cohorts and at the Early Detection Research Network. The 2014 PCTPT was compared to the ERSPC-RC stage 4 (ERSPC-RC4, prior negative biopsy) in 2016 by Poyet *et al.* This study of 996 men from a European tertiary care center found no significant difference for all prostate cancer (AUC 0.65 *vs* 0.66) but did find the ERSPC-RC4 to be superior in the detection of clinically significant prostate cancer (AUC 0.73 *vs* 0.70).[69] The model was again updated in 2018 based on data from 15,611 men in the PCGB and renamed the PBCGRC.[67] A retrospective study of 7119 men from 10 independent cohorts in Europe and Australia compared the ERSPC-RC4, PCPT 2018, and several other risk calculators. The study, like the 2016 Poyet *et al.*, found no difference in predicting any prostate cancer but did find the ERSPC-RC4 to be superior at identifying clinically significant prostate cancer with an AUC of 0.77.[70] One important finding from the PCPT and PCGB studies is that there is a decreased likelihood of a positive biopsy after a prior negative biopsy.

Although race had been included in previous prostate cancer risk assessments, the PCPT identified AA race as a predictor of high-grade disease. A similar simultaneous study done at several institutions in the United States analyzed 9473 patients at equal-access health care institutes created a nomogram that utilized AA race as a key predictor of prostate cancer. The nomogram utilized AA race, age, year of biopsy, PSA level, DRE, and number of cores taken to be statistically significant. The final predicted model had a concordance index of 75%. Of note, AA men in the study had significantly higher PSA levels than Caucasians.[71]

The inclusion of mpMRI has been shown to vastly improve prior negative biopsy risk calculators. van Leeuwen *et al.*'s model, based on 393 men from Australia, was the first to create a risk calculator for those with previous biopsy to include mpMRI. The risk calculator included PSA level, DRE, prostate volume, previous biopsy, and PIRADS score. The AUC for the model without mpMRI was 0.80, but increased to 0.88 with the inclusion of mpMRI.[32] In 2018, a nomogram created by Truong *et al.* was created from a retrospective two institution study in the United States from patients with at least one prior negative biopsy. Of the 285 patients, 135 had benign biopsy pathology. The

multivariate analysis found predictors of benign pathology to be associated with age, PSA, prostate volume, and PI-RADS score. The AUC for this study was found to be 0.825.[33] The Truong reported nomogram was then externally validated and updated by Bjurlin *et al.* in 2019 as a multi-institutional effort. Validation utilizing 2063 men across three different United States institutions found an AUC of 0.79.[34]

ERSPC-RCs were updated in 2019 to include mpMRI. Alberts *et al.* constructed MRI-ERSPC-RCs from 1225 Michigan men for the prediction of any and high-grade prostate cancer by adding PI-RADS and age as parameters to both ERSPC-RC3 and ERSPC-RC4. The AUC for ERSPC-RC3 (0.84 *vs* 0.76) and ERSPC-RC4 (0.85 *vs* 0.74) improved with the addition of mpMRI.[35]

Analysis of the ERSPC screening in Sweden in 2008 and later in France in 2010 derived an algorithm for predicting prostate cancer at biopsy by combining human kallikrein-related peptidase 2 to blood-total, free, and intact PSA or the 4Kscore. Comparing PSA alone in the cohort from Sweden to the 4 K score increased the AUC from 0.608 to 0.84.[72,73] Later, a 4 K nomogram based off 574 men in New York that included mpMRI found 4 K score, PI-RADS $\geqslant 4$, and a prior negative biopsy to be significant predictors of prostate cancer, clinically significant prostate cancer (Gleason score $\geqslant 3 + 4$), and unfavorable prostate cancer (Gleason score $\geqslant 4 + 3$). The AUC for these three were 0.84, 0.88, and 0.86 compared to 0.73, 0.80, and 0.81 for 4 K score alone.[36]

A group at Stanford University created a unique nomogram that utilized mpMRI to predict clinically significant prostate cancer with a prior biopsy history using 2125 men cared for across three different institutions. The group validated the study based on data sets at two other large academic institutions. The Stanford Prostate Cancer Calculator (SPCC) used biopsy history, PSA density, PIRADS score of 4 or 5, Caucasian race, and age as risk factors.[37] The AUC of the SPCC was 0.78, 0.85, and 0.80 at the three institutions. This study also noted that AA race did not confer a higher risk for prostate cancer. However, SPCC does not include men with a normal MRI, and they did not include family history in their model. An online version of this model is available.[74]

The Prospective Loyola University mpMRI (PLUM) Prostate Biopsy assessed for predictors of clinically significant prostate cancer in 900 men who were either biopsy-naive or had prior negative biopsies. Patients underwent mpMRI followed by TRUS fusion-guided biopsies with both systemic and targeted core PSA. Predictors for any cancer were found to include PSA, PSA density, prostate volume, and PI-RADS score. The study noted that family history and race were not associated with prostate cancer in the prior negative biopsy setting. The AUC for clinically significant prostate cancer of biopsy-naive patients was 0.877 with PI-RADS scoring and 0.814 without. In addition, the AUC for the prior biopsy group dropped from 0.869 to 0.775 with the removal of PI-RADS scoring. Regarding PI-RADS cut offs, for biopsy-naive patients a PI-RADS cutoff of 3 most closely approximated the model up to a threshold of 16% change of clinically significant prostate cancer. For the prior biopsy group, a PI-RADS cutoff of 4 was closest approximation up to the threshold of 27% chance of clinically significant prostate cancer. An online version of this model is also available.[38,75]

Active surveillance. Active surveillance (AS) provides select patients an option to delay or potentially avoid definitive treatment of their localized prostate cancer. AS protocols have generally been based on clinical parameters including PSA, clinical stage, and biopsy results. However, misassignment of patients into AS protocols that result in worse oncologic outcomes or exclusion of patients into AS protocols leading to overtreatment are all issues that continue to be active areas of debate. It has been hypothesized that the inclusion of clinically insignificant disease, Gleason 6 or Grade Group 1 (GG1) in these protocols and their use of predefined thresholds of each clinical variable, prevents an individualized assessment of a patient's candidacy for AS.[76,77] The inclusion of mpMRI and MRI-targeted biopsy has improved the prediction of upgrading Gleason score on confirmatory biopsy in men on AS.[78] Therefore, Lai *et al.* created a nomogram to predict prostate cancer upgrading in 76 men. Twenty-two (26.32%) men were upgraded with PSA density, duration between diagnosis and MRI/US fusion biopsies, PI-RADS, and total lesion density were independent risk factors for upgrading. Utilizing these factors, their model generated an AUC of 0.84 compared to an AUC of 0.69 with only PSA being utilizing.[39] Interestingly, the added information provided by mpMRI and targeted biopsy

pathology data has been shown to influence patient decision-making, as those that undergo MRI-targeted biopsy are more likely to choose AS than any definitive therapy when adjusting for age, PSA density, biopsy history, race, and prostate cancer grade group.[79,80]

Gandaglia *et al.* sought to establish a nomogram that would increase the number of patients eligible for AS without increasing the risk of unfavorable pathology or upgrading after RP. They analyzed 16,049 patients with low- or intermediate-risk prostate cancer at biopsy, who were then treated with RP. Of these, 5289 patients (33%) had unfavorable disease defined as lymphovascular invasion, non-organ confined disease, and/or GG $\geqslant$ 3. They too found that PSA, clinical stage, GG at biopsy, number of positive cores, and PSA density were independent predictors of unfavorable pathology ($p < 0.001$). These variables were included into their model with an AUC at internal validation of 0.752. Furthermore, they compared their model to known AS protocols from the Prostate Cancer Research International: Active Surveillance (PRIAS) criteria, Toronto, University of California at San Francisco, and Royal Marsden. While PRIAS criteria had the lowest rate of misclassification (13%) compared to the other established protocols, adoption of Gandaglia's model at an 18% threshold led to increase of eligible AS patients from 20.6% to 29.4% without increasing the risk of misclassification.[81] Lantz *et al.* externally validated the model created by Gandaglia's team, but also included MRI findings as well to improve the predictability of the model. External validation of the Gandaglia published model resulted in an AUC of 0.63. However, inclusion of MRI prostate volume, and MRI detection of extraprostatic extension increased the AUC to 0.71 as well as increased the proportion of AS eligible men from 45% to 77% with only a 1% increase in unfavorable pathology.[40]

Luzzago *et al.* also developed their own nomogram to identify candidates for AS that accounted for a patient's PSA density, GG, PI-RADS score, and MRI detection of extraprostatic extension. They compared their model to PAIS criteria, Johns Hopkins (JH), European Association of Urology (EAU) low-risk classification, and EAU low-risk or low-volume with GG2. After analysis of 1837 patients (42.2% had clinically significant prostate cancer at RP), Luzzago's model AUC of 0.84 outperformed the other criteria by 0.20.

This combined nomogram increased the eligibility of men for AS by ~25% and 35%, compared to the PRAIS and JH criteria, respectively. Furthermore, their model had lower rates of unfavorable pathology at RP compared to all established criteria. However, their model utilized cognitive fusion biopsy, and their data are not externally validated. Nevertheless, these models continue to support the integration and use of MRI and nomograms in AS protocols.[41]

Treatment planning. The assessment of tumor extension, risk of residual disease, and determine of whether to perform a pelvic lymph node dissection (PLND) in men with newly diagnosed localized prostate cancer is critical during treatment planning. The Partin tables and D'Amico models were one of first models to risk stratify prostate cancer and predict the probability of adverse pathology and recurrence, biochemical outcomes after RP, external beam radiation therapy, or interstitial brachytherapy radiation for clinically localized prostate cancer.[82–84] Since then, many nomograms have been built to assess for adverse pathologic features and lymph node invasion.[85]

The decision to perform PLND concurrently at time of RP in men with localized clinically significant prostate cancer must be carefully weighed. While PLND allows accurate nodal staging and guides the potential need for adjuvant treatment, the increased operative time and complications including lymphocele and lymphedema must be considered.[86] The Briganti nomogram is classically one of the most widely utilized nomograms to determine the need for PLND. Their landmark study noted 10.4% of patients having lymph node invasion at the time of surgery with PSA, Gleason score, clinical stage, and percentage of positive cores being independent predictors of lymph node invasion ($p < 0.001$).[87] Briganti *et al.* again updated their model in 2017 and reported a 90.8% predictive accuracy and at a 7% cutoff, they noted that 69% of PLND could be avoided with only missing 1.5% of patients with lymph node invasion.[88] In addition, the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram has also been widely utilized, given its easy-to-use online interface.[43] Therefore, current guidelines by the EAU and National Comprehensive Cancer Network have recommended that men with a high risk of lymph node invasion (>2–5%) pursue PLND. However, these models are based on historical cohorts that were diagnosed by only systematic biopsy. As previously discussed, the

combination of mpMRI and MRI-targeted biopsy detects more clinically significant tumors and reduces the detection of insignificant prostate cancer.[89] These advances have resulted in a treatment shift toward higher-risk disease in patients undergoing prostatectomy in contemporary cohorts.[90] Soeterik *et al.*[42] substituted clinical staging by DRE with mpMRI and noted a significant improvement of the AUC of both the MSKCC and Briganti 2012 nomograms in detected lymph node invasion. A new nomogram created by Gandaglia *et al.* incorporated men diagnosed with MRI-targeted biopsies in their study cohort of 497 men who underwent RP and PLND. With 65 (12.5%) patients having lymph node invasion, their model accounted for PSA, clinical stage detected by mpMRI, GG of targeted biopsy, lesion diameter according to mpMRI and percentage of core with clinically significant prostate cancer at systematic biopsy. The new model's AUC of 0.86, outperformed the AUC of the Brignati 2012 (0.82), Briganti 2017 (0.82), and MSKCC (0.81) models. Furthermore, at a 7% cutoff, utilization of this new nomogram avoided 57% of PLND while missing a lower number lymph node invasion (1.6% *vs* 4.6% *vs* 4.5% *vs* 4.2% for the novel, Briganti 2012, Briganti 2017, and MSKCC nomograms, respectively).[45] The Briganti 2019 model was externally validated with 487 men diagnosed *via* MRI-targeted biopsy and underwent RP and PLND. With 38 (8%) of men having lymph node invasion, the nomogram's AUC was 79% again outperformed prior models (75% *vs* 65% *vs* 74% for the Briganti 2012, Briganti 2017, and MSKCC nomograms, respectively). At the 7% cutoff, 273 (56%) of PLND would be avoided, while only missing 2.6% of men with lymph node involvement.[91]

At the time of surgical resection, it is imperative to understand the presence of adverse pathologic features including extracapsular extension (ECE) and seminal vesicle invasion (SVI) as they can guide the decision to pursue sparing of the neurovascular bundle and determine the need for adjuvant treatment.[92–94] The Partin tables and MSKCC nomograms have historically been used as a guide to predict the probability of ECE and SVI prior to prostatectomies; however, they do not utilize data provided by mpMRI.[95,96] While mpMRI has a moderate sensitivity in predicting ECE and SVI, it has been incorporated in some models and has increased the model's ability to predict adverse pathology.[46,97–99] Soeterik *et al.*

substituted clinical staging by DRE with mpMRI and noted a significant improvement of the AUC of both the MSKCC and Briganti 2012 nomograms in detected lymph node invasion. Rayn *et al.* incorporated data from mpMRI and MRI-targeted biopsy into the Partin tables and MSKCC nomogram. Incorporation of mpMRI resulted in significant increases in AUC for detecting organ defined disease, ECE, SVI, and lymph node invasion for both the MSKCC nomogram and Partin tables. The addition of including the Gleason score obtained from MRI-targeted biopsy resulted in increases in the AUC in predicting organ-confined disease and ECE in both nomograms.[47] Therefore, Gandaglia *et al.* developed a novel nomogram that incorporated men who underwent combined MRI-targeted and systematic biopsy to predict adverse pathologic features and prostatectomy. Of the 614 men included in the study, 333 (54%) had ECE, 88 (14%) had SVI, and 169 (27%) had upgrading of grade group at final pathology. The inclusion of mpMRI and MRI targeted with concomitant systematic biopsy into their model resulted in AUCs of 0.73 for ECE, 0.81 for SVI, and 0.73 for upgrading. Interestingly, while omitting systematic biopsy reduced the detection of clinically insignificant prostate cancer, inclusion into the model reduced the rates of upgrading at final pathology.[48] This model was externally validated with 566 men with 209 (37%) having ECE and 68 (12%) having SVI at final pathology. The new nomogram demonstrated higher discrimination (71.8% *vs* 69.8%, $p = 0.3\%$ and 71.8% *vs* 61.3%, $p < 0.001$) and similar net benefit for a probability threshold of at least 30% of predicting ECE when compared with MSKCC nomogram and Partin tables, respectively. Regarding SVI, the novel nomogram had comparable discrimination (68.5% *vs* 70.4% *vs* 67.8%, $p > 0.05$) and only a slight benefit for probability thresholds greater than 7.5% compared to the MSKCC nomogram and Partin tables, respectively. Disappointingly, this new novel nomogram did not distinctively improve the detection of ECE and SVI compared to prior models.[49] Whether there are other clinical factors influencing ECE and SVI, discrepancies between MRI and pathologic interpretations, or even mpMRI's moderate sensitivity in predicting these adverse pathologies remains to be seen. Nevertheless, these studies have demonstrated that incorporation of mpMRI and targeted biopsy in prostate cancer nomograms demonstrates some promise in selecting patients for PLND and predicting adverse pathologies for treatment planning.

Furthermore, nomograms have been created to help in the decision to perform incremental nerve-sparing prostatectomy. Severing the neurovascular bundles during RP can lead to poor outcomes such as urinary incontinence and erectile dysfunction.[100–102] Current AUA and European Association of Urology guidelines recommends against preserving the neurovascular bundle in cases with non-localized disease and the clinical stage >T2c with any biopsy Gleason score >7, respectively.[103–105] Nomograms have been generated to identify patients that have ECE and are therefore excluded from nerve-sparing procedures. Ohori *et al.*, Steuber *et al.*, and Patel *et al.* created nomograms to identify ECE, with AUC's for identifying ECE ranging from 0.78 to 0.81.[106–108] As mpMRI becomes more common in preoperative setting, new nomograms that utilized mpMRI focused on higher GG as well as prostates that underwent targeted biopsy, unlike prior nomograms. Due to mpMRI's low per-patient sensitivity for the detection of ECE at 57%, nomograms can provide superior preoperative planning.[97] A nomogram by Martini *et al.* in 2018 from 829 New York patients utilized PSA level, clinical stage, biopsy findings, and mpMRI. This nomogram had an internalized AUC of 82%.[46] Of note, there is currently no consensus on the grading system that should be used for nerve-sparing tumor's operability. For example, Patel *et al.* used a five inverse grade scale corresponding to the extra fascial dissection. Whereas, Martini *et al.*[109] used a grading system based on the multilayered structure of the lateral prostatic fascia. In 2020, Soeterik *et al.* noted the small number of nomograms for identifying nerve-sparing procedures and created their own from 887 Dutch patients using PSA density, DRE staging, mpMRI staging, ISUP grades 3–5, and percentage of positive cores. The AUC for their model was 0.82 on internal validation and 0.83 and 0.78 on external validation at two other Dutch hospitals.[50]

Discussion

The future of nomogram use in clinical decision-making in prostate biopsies is bright. The inclusion of mpMRI findings and MRI-targeted biopsy pathology data into prostate cancer nomograms has greatly enhanced the available tools that clinicians have in weighing the decision to pursue a prostate biopsy for their patients. Online calculators such as those provided by the PCPTRC, PBCGRC, SPCC, and PLUM allow providers

and their patient's easy access to the risk assessments these models provide. However, careful consideration of the patient populations that are included in these studies and whether these studies have been extensively externally validated must be carefully weighed before utilizing them.[37] Further considerations in assessing these models in younger men at risk for prostate cancer should be considered for the future as the decision to pursue active treatment *versus* AS for a newly diagnosed prostate cancer has a significant impact on their quality of life.[110]

Unfortunately, nomograms need to be extensively validated, and re-calibrated to each new population.[111–113] This can be costly and time-consuming. The generation of nomograms is very dependent on the population used to create the nomogram as well as the size of the population to work with. This is where a potential for national/international large database could be generated. Adding information to established online databases, could provide researchers more access to either create or externally validate their nomograms on an equal data set to enhance generation and comparisons between nomograms. In addition to validation, more studies should include cost effectiveness for incentivizing the advancements of nomograms. However, the reduced biopsy rate and potential downstream savings that result from less overtreatment offer potential cost savings that may offset the additional costs of utilizing MRI.[114] Of note, there has been no studies that survey current urologists about which nomogram they prefer to use and how often they use it. Such data could help guide more readily available nomograms, such as pre-calculated in the EMR or readily available online calculators. Nevertheless, utilizing advanced imaging, such as mpMRI, can improve the individual risk assessment, and can strengthen the shared decision-making process by well-informed patients and their clinician care providers.[115]

Conclusion

Prostate cancer nomograms are simple methods of improving the accuracy of predicting clinically significant prostate cancer as compared single modality studies. There are currently many nomograms available for the physician to use. These have shown success at predicting clinically significant prostate cancer in several patient cohorts. Although, only a few of these nomograms have

been externally validated. Further studies are needed to find which nomograms are the most accurate and which nomograms physician choose to use.

Author contribution(s)

Garrett J. Brinkley: Data curation; Writing – original draft; Writing – review & editing.

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Funding

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Soroush Rais-Bahrami serves as a consultant to Philips/InVivo Corp, Genomic Health Inc, Blue Earth Diagnostics, Bayer Healthcare, UroViu Corp, and Intuitive Surgical.

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