

Magnetic Resonance Imaging-Defined Prostate-Specific Antigen Density Significantly Improves the Risk Prediction for Clinically Significant Prostate Cancer on Biopsy



Nisha R. Bhat, Joel M. Vetter, Gerald L. Andriole, Anup S. Shetty, Joseph E. Ippolito, and Eric H. Kim

OBJECTIVE To evaluate the predictive value of magnetic resonance imaging (MRI)-defined prostate-specific antigen (PSA) density and MRI interpretation for the detection of clinically significant prostate cancer (PCa).

METHODS We retrospectively reviewed our institutional database of men who received prostate MRI prior to biopsy at our institution between September 2014 and December 2016, excluding those on active surveillance ($n = 372$). Logistic regression models to predict clinically significant PCa on biopsy were developed using (1) MRI-defined PSA density; (2) PSA alone; and (3) the Prostate Cancer Prevention Trial (PCPT) risk calculator. Additional logistic regression models were then generated by combining the previous clinical variables with MRI interpretation (ie, prostate imaging reporting and data system [PI-RADS] classification): (1) MRI-defined PSA density + MRI interpretation; (2) PSA + MRI interpretation; and (3) PCPT + MRI interpretation. Receiving operator characteristic curves for each of the 6 models were generated, and the area under the curves (AUC) were compared.

RESULTS MRI-defined PSA density (AUCPSAD = 0.77) significantly outperformed the PSA (AUC-PSA = 0.66, $P < .01$) and PCPT models (AUCPCPT = 0.70, $P < .01$). When combined with MRI interpretation (ie, PI-RADS classification), the MRI-defined PSA density model (AUC-PSAD + MRI = 0.80) significantly outperformed the PSA (AUCPSA + MRI = 0.75, $P < .01$) and PCPT models (AUCPCPT + MRI = 0.76, $P = .01$).

CONCLUSION In addition to the PI-RADS classification, prebiopsy multiparametric magnetic resonance imaging also provides an accurate assessment of prostate volume. By utilizing this additional data to determine MRI-defined PSA density, we find that risk discrimination for clinically significant PCa on biopsy can be significantly improved. UROLOGY 126: 152–157, 2019. © 2018 Elsevier Inc.

For 3 decades, transrectal ultrasound (TRUS) guided biopsy has been the standard for diagnosis of prostate cancer (PCa) in men who present with elevated prostate-specific antigen (PSA), but major limitations of this conventional diagnostic algorithm are now apparent. PSA is a poor discriminant of PCa risk; as a result, many men without cancer undergo unnecessary biopsies.¹ Additionally, the imprecision of TRUS-biopsy likely results in the overdiagnosis of low risk disease (eg,

Gleason 6 PCa) while missing high-grade tumors. As a result, multiparametric magnetic resonance imaging (mpMRI) has emerged as a useful tool to improve PCa detection. MRI-targeted biopsies have been shown to significantly improve the detection of clinically significant PCa while reducing the detection of low-risk PCa when compared to conventional TRUS biopsy.^{2–5} Additionally, it has been demonstrated that mpMRI accurately detects and localizes clinically significant PCa lesions.⁶

However, the negative predictive value of MRI to exclude clinically significant cancer (Gleason score ≥ 7) has been estimated to be at or less than 90%, suggesting that, while MRI may have utility as a screening tool, unsuspecting MRI alone cannot reliably exclude significant disease.^{7,8} Thus, combining prebiopsy MRI data with other clinical information is critically important to improve the accuracy of PCa risk prediction. Prebiopsy

Financial Disclosure: The authors declare that they have no relevant financial interests.

From the Division of Urology, Washington University School of Medicine, St. Louis, MO; and the Department of Radiology, Washington University School of Medicine, St. Louis, MO

Address correspondence to: Eric H. Kim, M.D., Division of Urology, Washington University School of Medicine, 4960 Children's Place, Campus Box 8242, St. Louis, MO 63110. E-mail: ehkim@wustl.edu

Submitted: July 20, 2018, accepted (with revisions): December 11, 2018

MRI imaging allows for easily accessible, noninvasive prostate volume assessment, which may be used to determine PSA density (defined by the quotient of PSA and prostate volume). PSA derivatives, such as PSA density, have been shown to enhance the performance of PSA for detecting PCa.⁹ Furthermore, recent studies have demonstrated that PSA density may inform biopsy decisions better than PSA alone.^{10,11} The aim of the present study was to determine the combined predictive value of MRI-defined PSA density and mpMRI interpretation.

MATERIALS AND METHODS

With Institutional Review Board approval, we retrospectively reviewed our institutional database of men who received prostate mpMRI between September 2014 and December 2016. We identified 455 patients who underwent prostate mpMRI prior to biopsy. We excluded patients with known PCa prior to their biopsy ($n = 83$) for a total cohort of 372 patients (biopsy naïve $n = 195$, previous negative biopsy $n = 177$).

mpMRI Technique

Specific description of our institutional prostate mpMRI technique has been published previously.¹² Briefly, all patients underwent 3-Tesla mpMRI using a pelvic phased-array coil on Siemens Trio and Skyra platforms (Siemens Healthcare, Erlangen, Germany). High-resolution turbo spin echo T2-weighted images consisted of 3-mm slice thickness, small field of view imaging (160 mm) with a matrix of 512×512 for axial imaging and 640×640 for coronal imaging. The small field of view diffusion-weighted imaging sequence initially consisted of 3 b-values: 50, 500, and 1000 with a matrix of 128×128 and 3-mm slices, and more recently b-values of 50 and 800 with a calculated b-value of 1400. Apparent Diffusion Coefficient maps were generated by the scanner. Dynamic contrast enhancement sequences consisted of 3D gradient recall echo T1-weighted images with a temporal resolution of 68 seconds, imaged initially over 6 minutes, later shortened to 2 minutes, with a matrix of 256×256 and 3-mm slice thickness.

mpMRI Interpretation

The Prostate Imaging Reporting and Data System (PI-RADS) version 1 was implemented at our institution in September 2014, followed by PI-RADS version 2 in February 2015.¹³ Although there are differences between the earlier and current scoring systems, recent studies have shown excellent inter-reader agreement for both scoring systems.¹⁴ Prostate volume was routinely measured using the semi-automated 3D segmentation feature of DynaCAD (Invivo Corporation, Gainesville, FL). Prostate mpMRI at our institution were read as part of the clinical workflow for the abdominal imaging section; 9 attending radiologists with an average of 11 years clinical experience after training and approximately 80 scans per year interpreted the studies. Radiologists had access to all available

clinical data in the patient chart at the time of interpretation, including previous biopsy results.

Biopsy Technique

For patients with PI-RADS classification 3 or greater lesions, software fusion MRI-targeted biopsy as well as standard 12-core systematic template biopsy were performed using the UroNav platform (Invivo Corporation, Gainesville, FL). The MRI-targeted biopsies included 3-4 cores at each lesion, based on lesion size. For patients with PI-RADS classification 1 or 2 mpMRI, a standard 12-core systematic template biopsy was performed.

Statistical Analysis

The Prostate Cancer Prevention Trial (PCPT) risk calculator 2.0 was used to calculate the PCPT risk estimate for high grade (Gleason ≥ 7) PCa on biopsy.¹⁵ MRI-defined PSA density was calculated as the quotient of the prebiopsy serum PSA and prostate volume calculated by mpMRI. Univariate logistic regression models to predict clinically significant PCa (Gleason ≥ 7) on biopsy were developed with PSA, MRI-defined PSA density, and the PCPT risk estimate. Additional multivariate logistic regression models were then developed combining the above variables with the PI-RADS classification ("MRI interpretation"). The MRI interpretation was treated as a binary variable with PI-RADS classification 4 or 5 considered positive. Receiver operating characteristic (ROC) curves were generated for all of the above models. Area under the curves (AUC) were compared using the Delong method. The P values less than .05 were considered statistically significant. All analyses were performed with R version 3.2.2.

RESULTS

Supplementary Table 1 summarizes the clinical characteristics and biopsy outcomes of the study cohort. The mean age of the study cohort was 64.7 years, the mean PSA was 9.4 ng/mL, the mean PCPT risk estimate was 12.9%, and the mean MRI-defined PSA density was 0.20 ng/mL². The majority of patients ($226/372 = 60.8\%$) were considered to have a positive mpMRI (PI-RADS classification 4 or 5). Overall, 41% of patients ($154/372$) were found to have clinically significant PCa (Gleason ≥ 7) on biopsy.

All regression models were found to be independently predictive of clinically significant PCa on biopsy: (1) PSA only (OR 1.12, $P < .001$); (2) PCPT only (OR 1.07, $P < .001$); (3) MRI-defined prostate density (OR 1.08, $P < .001$); (4) PSA + MRI (OR 1.11, $P < .001$); (5) PCPT + MRI (OR 1.06, $P < .001$); (6) MRI-defined prostate density + MRI (OR 1.07, $P < .001$).

The ROC curves and AUC for the above models are provided in Figure 1. The MRI-defined PSA density model ($AUC_{PSAD} = 0.77$) significantly outperformed both the PSA ($AUC_{PSA} = 0.66$, $P < .01$) and PCPT models ($AUC_{PCPT} = 0.70$, $P < .01$). The addition of the MRI interpretation (PI-RADS classification) significantly improved the risk prediction of each of the clinical models

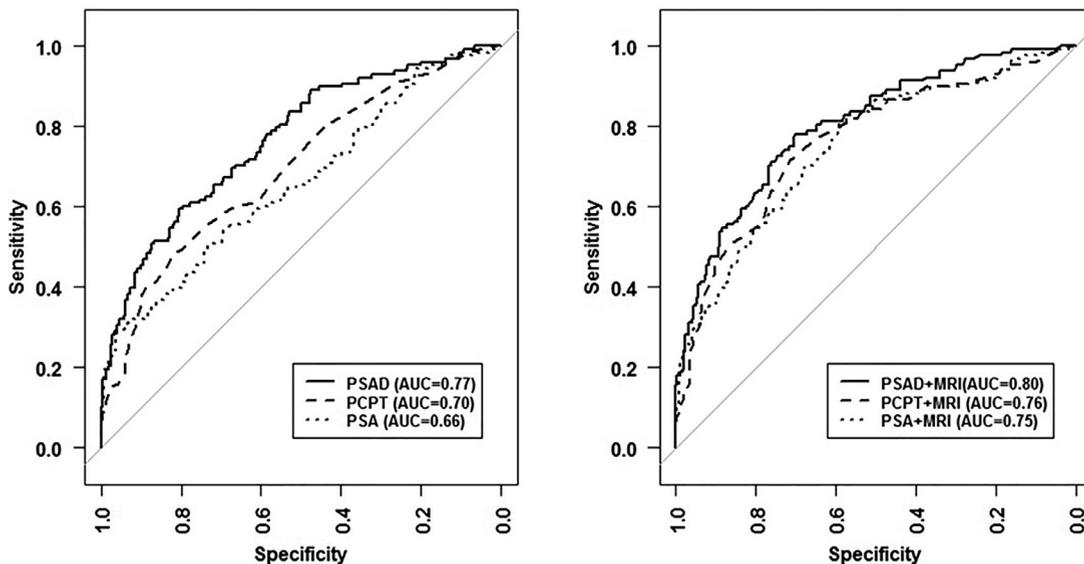


Figure 1. ROC curves with AUC for the multivariate regression models.

($AUC_{PSAD+MRI} = 0.80$ and $AUC_{PSAD} = 0.77$, $P = .04$; $AUC_{PSA+MRI} = 0.75$ and $AUC_{PSA} = 0.66$, $P < .01$; $AUC_{PCPT+MRI} = 0.76$ and $AUC_{PCPT} = 0.70$, $P < .01$). The greatest AUC was achieved when MRI suspicion was combined with MRI-defined PSA density ($AUC_{PSAD+MRI} = 0.80$). When combining the MRI interpretation (PI-RADS classification) to the clinical models, the MRI-defined PSA density model ($AUC_{PSAD+MRI} = 0.80$) significantly outperformed the PSA ($AUC_{PSA+MRI} = 0.75$, $P < .01$) and PCPT models ($AUC_{PCPT+MRI} = 0.76$, $P = .01$). Thus, the greatest AUC was achieved when MRI suspicion was combined with MRI-defined PSA density ($AUC_{PSAD+MRI} = 0.80$).

Head-to-head comparisons of the models are summarized in [Table 1](#), with P values of head-to-head AUC comparisons provided in each cell. Each subsequent model (going by row or column) demonstrates significantly higher AUC, except in 3 cases. We find that the PSA + MRI interpretation and the PCPT + MRI interpretation models perform similarly to the MRI-defined PSA density model. We also find that the PSA + MRI interpretation and the PCPT + MRI interpretation models perform similarly.

The same models for subsets of our study cohort based on biopsy status are provided in [Figure 2](#) (biopsy naïve patients) and [Figure 3](#) (previous negative biopsy patients). For the biopsy-naïve patients, the MRI-defined PSA

density + MRI interpretation model ($AUC = 0.83$) significantly outperformed all other models except the PCPT + MRI interpretation model ($AUC = 0.79$, $P = .16$). For the previous negative biopsy patients, the MRI-defined PSA density + MRI interpretation model ($AUC = 0.78$) performed similarly to the MRI-defined PSA density model ($AUC 0.78$, $P = .91$).

DISCUSSION

In this study, we first compared the predictive performance of 3 PCa risk models based upon clinical parameters: (1) MRI-defined PSA density; (2) PSA alone; and (3) the PCPT risk calculator. We found that the MRI-defined PSA density model significantly outperformed both the PSA and PCPT models in predicting clinically significant PCa. Using these clinical parameters in combination with the MRI interpretation (ie, PI-RADS classification), 3 additional models were generated: (1) MRI-defined PSA density + MRI; (2) PSA + MRI; and (3) PCPT + MRI. The addition of MRI interpretation significantly improved the predictive performance of all of the clinical parameters, and the MRI-defined PSA density + MRI interpretation model significantly outperformed all other models. Biopsy-naïve patients appeared to derive the most benefit from the combined MRI-defined PSA density + MRI interpretation model. For patients with

Table 1. Head-to-head comparison of AUCs of all models using the Delong method (p values)

Models	PSA	PCPT	PSAD	PSA + MRI	PCPT + MRI	PSAD + MRI
PSA	-	0.028	<0.001	<0.001	<0.001	<0.001
PCPT	0.028	-	0.006	0.013	<0.001	<0.001
PSAD	<0.001	0.006	-	0.534	0.893	0.042
PSA + MRI	<0.001	0.013	0.534	-	0.189	<0.001
PCPT + MRI	<0.001	<0.001	0.893	0.189	-	0.011
PSAD + MRI	<0.001	<0.001	0.042	<0.001	0.011	-

PSA, prostate-specific antigen; PCPT, Prostate Cancer Prevention Trial, PSAD, MRI-defined PSA density, AUC, area under the curve.

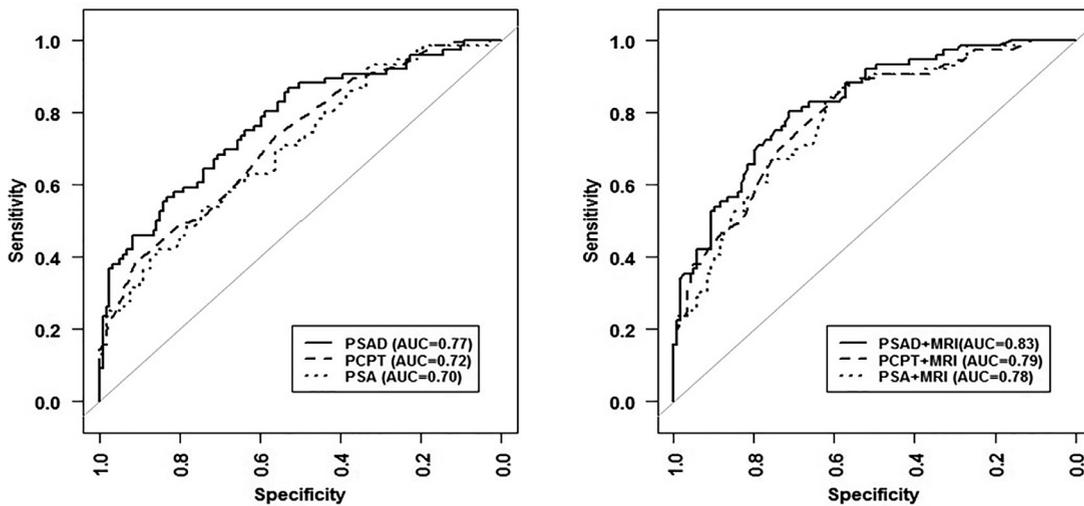


Figure 2. ROC curves for the regression models for biopsy naive patients.

previous negative biopsy, the MRI-defined PSA density model performed similarly to the combined MRI-defined PSA density + MRI interpretation model.

Our findings underscore the potential utility of MRI-defined PSA density in avoiding unnecessary biopsies. The poor specificity of PSA-driven PCa screening results in many patients without clinically significant PCa receiving prostate biopsies, which are invasive, costly, and associated with risks such as sepsis and bleeding.^{16,17} Though imaging prior to prostate biopsy has yet to be widely implemented, mpMRI has shown high PCa diagnostic accuracy and demonstrated improved discrimination between clinically significant PCa and benign disease when compared to PSA.³ Importantly, mpMRI also allows for easily accessible and accurate prostate volume measurements that can be used to determine PSA density.

Studies evaluating the accuracy of prostate volume estimates in patients receiving both TRUS and MRI prior to radical prostatectomy have found that MRI measured prostate volume has greater accuracy than TRUS estimates.¹⁸ Thus, PSA density calculated using MRI measured prostate volume are more precise.

In this study, we found that MRI-defined PSA density was a better discriminant between benign PSA elevation (often associated with large prostate volume) and clinically significant cancer than serum PSA alone. Notably, we also found that MRI-defined PSA density significantly outperformed the PCPT model (AUC 0.77 vs 0.70, $P < .01$), highlighting the importance of including prostate volume in PCa risk assessment. Recent literature supports the superior predictive value of PSA density when compared to serum PSA for PCa detection.¹⁹ When Jue et al evaluated the performance of

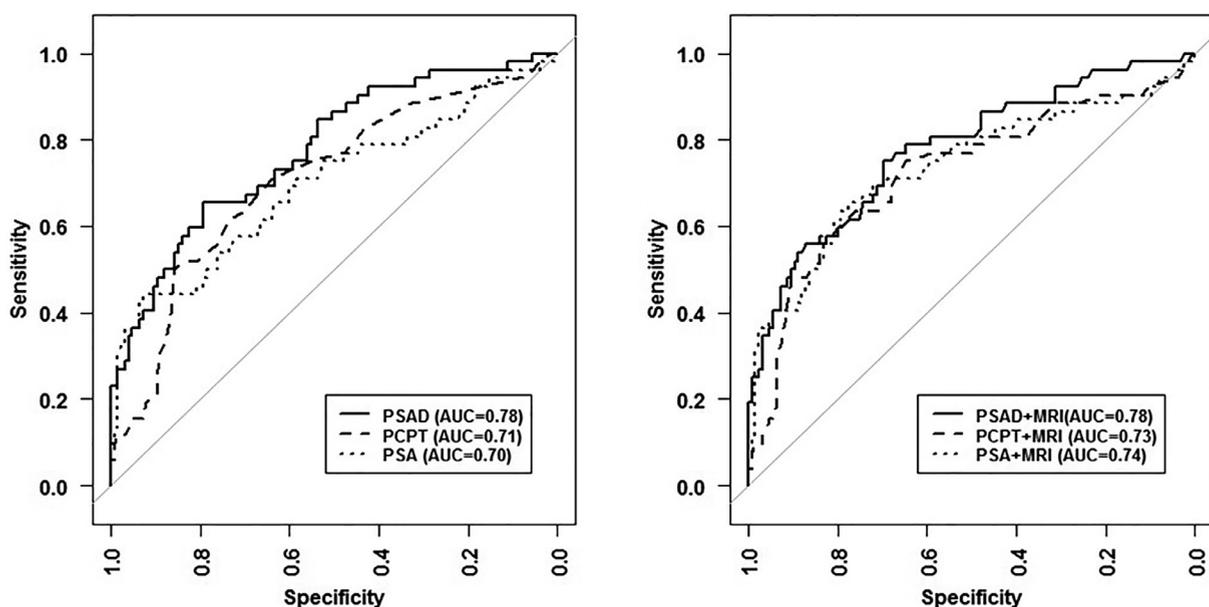


Figure 3. ROC curves for the regression models for previous negative biopsy patients.

PSA density and PSA for PCa detection in a prospective cohort of men who were undergoing extended template biopsy of the prostate, they observed that PSA density performed better than PSA in detecting any PCa (AUC 0.72 vs 0.67, $P = .001$).¹⁰ While MRI-defined PSA density significantly outperformed serum PSA and PCPT in our series, the relatively low predictive performance (AUC = 0.77) of MRI-defined PSA density suggests that it may be most clinically useful when combined with other parameters. The addition of mpMRI interpretation did improve predictive performance (AUC = 0.80); however, this difference may not be clinically significant (Δ AUC = 0.03). As the field continues to evolve, clinically meaningful risk prediction models will likely require multiple inputs, including mpMRI interpretation, clinical variables, and potentially reflex test results (eg, urine and serum biomarkers).

Although mpMRI alone has demonstrated high sensitivity for detection of clinically significant PCa, studies evaluating the negative predictive value of unsuspected mpMRI have reported a range of values, making its use as a triage test for prostate biopsy questionable. A meta-analysis assessing the performance of mpMRI for detecting PCa reported a specificity of 0.88, sensitivity of 0.74, and NPV of 0.64–0.94.²⁰ In our cohort, 21 of 146 patients with unsuspected mpMRI (PI-RADS ≤ 3) were found to have clinically significant PCa (Gleason ≥ 7) on biopsy (NPV = 84%). We find that the risk discrimination for clinically significant PCa is significantly improved by combining either MRI-defined PSA density or the PCPT risk estimates with the mpMRI information. This suggests that an integrative approach that combines MRI interpretation with clinical factors such as PSA density may be clinically useful in determining which patients may safely avoid biopsy. We have previously demonstrated the added value for mpMRI for patients with PCPT estimated risk of high-grade disease less than or equal to 10%.²¹ In a similar fashion, MRI-defined PSA density may be combined with clinical history (eg, age, race, family history) as well as mpMRI findings to provide further improvements in risk discrimination.

The highest AUC was observed when MRI-defined PSA density was combined with MRI interpretation. However, upon subgroup analysis, we found that the incremental gain in performance between MRI-defined PSA density and the combined MRI-defined PSA density + MRI interpretation model was only significant in biopsy naïve patients. For patients with previous negative biopsy, the combined model did not outperform the MRI-defined PSA density model. Patients with larger prostates are likely to have elevated PSA and are more likely to undergo multiple prostate biopsies. In this study, patients with previous negative biopsy had a significantly higher mean MRI-defined prostate volume than biopsy naïve patients (68.3 vs 49.5, $P < .001$). Our results underscore the importance of PSA density determination in preventing repeated invasive testing for these patients, whose PSA, though elevated, is appropriate for their prostate size. For biopsy naïve patients, combining MRI findings with MRI-defined PSA-density

may better identify patients with very low risk of PCa who can safely avoid biopsy.

To better quantify the value of prostate mpMRI, we compared the best model that includes MRI information (eg, the MRI-defined PSA density + MRI interpretation model) to the PSA alone model. The absolute difference in AUC between these curves (0.80 vs 0.66) is difficult to place into context. By taking the maximal inflection point on the ROC curves between the 2 models, we find that the difference in AUC of 0.14 is associated with a number needed to treat of approximately 7. This finding would suggest that for every 7 patients who receive a prostate mpMRI (thus MRI-defined PSA density and MRI interpretation are available) the accurate prediction of clinically significant PCa on biopsy is improved for 1 patient. Therefore, for every 7 patients that we base our decision to perform biopsy on the MRI-defined PSA density + MRI interpretation model (rather than PSA alone), we expect that we will diagnose 1 additional case of clinically significant PCa or successfully avoid 1 unnecessary biopsy (benign or low-risk PCa).

The present study is not without limitations. The retrospective nature of the study introduces sources of bias that cannot be completely accounted. Biopsy results were used for observed clinically significant PCa; however, the gold standard for pathologic determination would be radical prostatectomy. The use of biopsy results is more generalizable as not all patients receiving mpMRI and biopsy, including some patients who are diagnosed with PCa, do not go on to radical prostatectomy. Furthermore, models based only on patients who received radical prostatectomy are likely biased to demonstrate improved prediction of clinically significant PCa. MRI interpretation included in this study was performed as part of the clinical workflow of the abdominal imaging section. Although this introduces variability based on radiologist to radiologist differences in interpretation, this method of prostate mpMRI interpretation is more generalizable to clinical practice across the country. Finally, the models presented in this study were based on the observed biopsy outcomes at our institution, and thus must be validated in independent cohorts prior to routine clinical use.

CONCLUSIONS

In addition to the degree of suspicion (ie, PI-RADS classification), prebiopsy mpMRI provides a convenient and accurate prostate volume assessment. By utilizing this additional data to determine MRI-defined PSA density, we find that risk discrimination for clinically significant PCa on biopsy can be significantly improved compared to other clinical determinants.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2018.12.010>.

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