

Restriction Spectrum Imaging as a Quantitative Biomarker for Prostate Cancer With Reliable Positive Predictive Value

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Study Need and Importance: The accuracy of the Prostate Imaging Reporting and Data System for clinically significant prostate cancer (csPCa) varies widely depending on which radiologist interprets a prostate MRI. Clinicians need an objective and easily interpretable form of MRI to estimate the probability of csPCa on biopsy.

What We Found: We studied an advanced form of MRI called restriction spectrum imaging (RSI) that is based on biophysics and adds as little as 2 to 3 minutes to a prostate MRI scan on modern clinical scanners. The RSI restriction score (RSIrs) is a quantitative MRI biomarker calculated from RSI that highlights regions of the prostate that may be cancerous (ie, hypercellular tissue with a high nucleus:cytoplasm ratio). These RSIrs maps are easily interpretable. The maximum RSIrs value within a patient's prostate directly relates to the probability of csPCa. In MRI data from 1892 patients across 7 institutions, RSIrs demonstrated strong and consistent detection of csPCa. Maximum RSIrs in the prostate (objectively) predicted biopsy outcomes with performance comparable with expert radiologists' interpretations of full multiparametric MRI examinations. The combination of RSIrs and Prostate Imaging Reporting and Data System outperformed either alone. RSIrs is also strongly associated with grade of cancer (Figure).

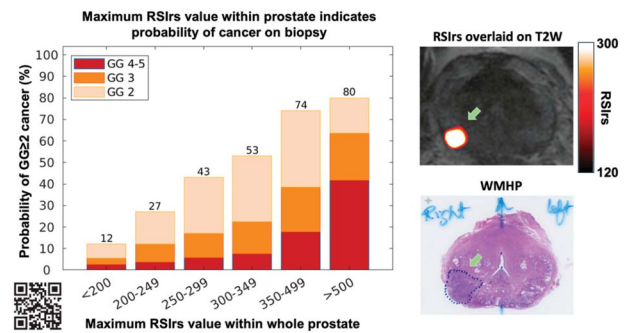




Figure. Left, Probability of grade group (GG) ≥ 2 cancer is directly related to the maximum restriction spectrum imaging restriction score (RSIrs) value detected within a patient's prostate. RSIrs maximum values are also associated with cancer grade. Right, Example of RSIrs overlaid on T2-weighted (T2W) prostate MRI before radical prostatectomy and the corresponding whole-mount histopathology (WMHP) specimen with GG3 tumor outlined.

Limitations: Limitations of the study include lack of central radiology and pathology review, biopsy as an imperfect gold standard, and exclusion of patients with hip implants due to potential for image artifacts.

Interpretation for Patient Care: Incorporating RSIrs into clinical workflows could enhance objectivity in prostate MRI, potentially helping both expert and nonexpert centers improve diagnostic confidence.

Restriction Spectrum Imaging as a Quantitative Biomarker for Prostate Cancer With Reliable Positive Predictive Value

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Purpose: The positive predictive value of the Prostate Imaging Reporting and Data System (PI-RADS) for clinically significant prostate cancer (csPCa, grade group [GG] ≥ 2) varies widely between radiologists. The restriction spectrum imaging restriction score (RSIrs) is a biophysics-based metric derived from diffusion MRI that could be an objectively interpretable biomarker for csPCa. We aimed to evaluate performance of RSIrs for patient-level detection of csPCa in a large and heterogenous dataset, and to combine RSIrs with clinical and imaging parameters for csPCa detection.

Materials and Methods: At 7 centers, participants underwent prostate MRI between January 2016 and March 2024. We calculated patient-level csPCa probability based on maximum RSIrs in the prostate and compared patient-level csPCa detection to apparent diffusion coefficient (ADC) and PI-RADS using AUC. We also evaluated csPCa discrimination by GG and combining RSIrs with clinical risk factors through multivariable regression.

Results: Among patients who met the inclusion criteria ($n = 1892$), probability of csPCa increased with higher RSIrs. Among biopsy-naïve patients ($n = 877$), AUCs for GG ≥ 2 vs non-csPCa were RSIrs = 0.73 (0.69-0.76), ADC = 0.54 (0.50-0.57), and PI-RADS = 0.75 (0.71-0.78). RSIrs significantly outperformed ADC ($P < .01$) and was comparable with PI-RADS ($P = .31$). RSIrs and PI-RADS

combined outperformed either alone. The model with RSIRs, PI-RADS, age, and PSA density achieved the best discrimination of csPCa.

Conclusions: RSIRs is an accurate and reliable quantitative biomarker that performs better than conventional ADC and comparably with expert-defined PI-RADS for patient-level detection of csPCa. RSIRs provides objective estimates of probability of csPCa that do not require radiology expertise.

Key Words: diffusion-weighted imaging, prostate cancer detection, prostate MRI, quantitative biomarker, restriction spectrum imaging

MULTIPARAMETRIC MRI (mpMRI) has reduced unnecessary biopsies, decreased overdiagnosis of indolent disease, and improved detection of clinically significant prostate cancer (csPCa, grade group [GG] ≥ 2).¹ In clinical practice, the Prostate Imaging Reporting and Data System (PI-RADS v2.1) is used to qualitatively interpret mpMRI. MRI has high sensitivity for csPCa, but its specificity is moderate² with widely variable readings across institutions and radiologists.^{3,4} The heavy dependence on user expertise and the variability across readers lead to health care disparities by limiting access to high-quality MRI. Quantitative imaging biomarkers reproducibly reflect underlying biology without reliance on subjective interpretation^{5,6} and could help move prostate MRI toward objective interpretation and consistent positive predicate value (PPV) for csPCa-positive biopsy.

Diffusion-weighted MRI is the most important mpMRI sequence for csPCa detection in the PI-RADS system.⁷ However, the conventional

quantitative metric for diffusion-weighted MRI, apparent diffusion coefficient (ADC), is based on an unrealistically simplistic model that assumes uniform-free diffusion of water molecules in the prostate. Restriction spectrum imaging (RSI) is a more advanced diffusion-weighted MRI technique that yields a quantitative biomarker (RSI restriction score [RSIRs]) designed to highlight csPCa. Previous retrospective single-center studies showed that RSIRs outperformed ADC for voxel-level and patient-level detection of csPCa.^{8,9} A prospective study found that radiation oncologists were much more accurate outlining csPCa on MRI with RSIRs than with conventional MRI alone.¹⁰

We evaluate RSIRs as a generalizable tool for objective patient-level csPCa detection in data from multiple imaging protocols, scanners, and vendors. We also investigate integrating RSIRs with clinical and imaging parameters to yield objective estimates of csPCa probability that could serve as a standardized

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Data acquisition: All authors.

Data analysis and interpretation: Seibert, Rojo Domingo.

Critical revision of the manuscript for scientific and factual content: All authors.

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Data manipulation: All authors.

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Revision: All authors.

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reference for assessing prostate MRIs, independent of radiologist expertise.

MATERIALS AND METHODS

Study Population

The data for this study come from 7 imaging centers in the Quantitative Prostate Imaging Consortium: Center for Translational Imaging and Precision Medicine at the University of California San Diego (UCSD) Health, University of California San Francisco, Harvard Massachusetts General Hospital, University of Rochester Medical Center, University of Texas Health Sciences Center San Antonio, and University of Cambridge. The study was approved by each center's Institutional Review Board. Participants in University of California San Francisco and University of Texas Health Sciences Center San Antonio provided written informed consent as part of other studies.^{11,12} A waiver of consent was approved by the respective Institutional Review Boards at the other centers for secondary use of routine clinical data. Data from UCSD Health and Center for Translational Imaging and Precision Medicine at the University of California San Diego are from a prospectively maintained database.

We included men of 18 years or older who underwent MRI for suspected or known csPCa between January 2016 and March 2024. We included participants without prior diagnosis (eg, elevated PSA), those planning to undergo cancer treatment, and those on active surveillance for lower-grade (GG1 and favorable GG2) cancer. Diagnosis of csPCa was confirmed on biopsy histopathology per clinical routine at each center. Patients were included if they had a biopsy within 6-month post-MRI or no biopsy but minimal risk for csPCa (PI-RADS 1-2 and PSA density [PSAD] ≤ 0.15 , which is a conservative PSAD cutoff¹³). Patients were excluded if they received prostate cancer (PCa) treatment before MRI or if they had metal implants because of the potential to cause significant artifact in MRI.

RSI Data Acquisition, Processing, and Modeling

Image postprocessing for RSI data included correction for background noise, gradient nonlinearities, and eddy currents.^{14,15} Data from UCSD Health were corrected for distortion caused by B_0 inhomogeneity.¹⁶ Automated prostate contours, generally highly accurate,¹⁷ were obtained using an Food and Drug Administration–cleared commercial product (OnQ Prostate, CorTechs.ai).

In the RSI framework, the diffusion MRI signal is modeled as a combination of exponential decays (Supplementary Table 1, <https://www.jurology.com>) corresponding to 4 diffusion microcompartments (intracellular, extracellular, free diffusion, and vascular flow) within each voxel.¹⁸ The biomarker is the intracellular signal at a given voxel normalized by the median T_2 -weighted signal in the prostate. RSIs is based on biophysics: It is highest where intracellular diffusion restriction (hypercellularity) and nucleus-to-cytoplasm ratio are high, both features characteristic of csPCa. Maximum RSIs is the highest RSIs value within the prostate.^{8-10,14,18-20} Postprocessing and analyses were performed in custom MATLAB scripts (MathWorks).

Patient-Level Detection of csPCa

For objective and reliable interpretation of MRI independent of radiologist expertise, risk of csPCa must be determined without subjective lesion delineation. We assessed csPCa classification performance using maximum RSIs, which only requires automated segmentation of the prostate. We plotted histograms of maximum RSIs by csPCa status and obtained the probability (PPV) of csPCa for RSIs strata by dividing the number of $GG \geq 2$ and $GG \geq 3$ cases, respectively, by the total number of patients for each bin. Bins spanned 50 RSIs units, and adjacent bins were combined for illustration purposes if PPV were similar. Our primary analysis was $GG \geq 2$ detection; secondary analyses were for $GG \geq 3$ and other subsets: by GG, age, and lesion zone. We showed the GG distribution within each RSIs stratum among biopsy-naïve patients at time of MRI. To evaluate patient-level detection of csPCa, we plotted the ROC curves with csPCa as the outcome of interest. We obtained ROC curves for maximum RSIs and for 99th and 98th percentiles of RSIs to demonstrate that most patients with high maximum RSIs also have many voxels with high RSIs.

Multivariable Integrated Risk

We used logistic regression models to predict the presence of csPCa based on imaging parameters and routinely available clinical risk factors that physicians may consider in biopsy decisions. Specifically, we combined RSIs and expert interpretation of MRI (PI-RADS) with objective variables: age, PSA level, PSAD, and self-reported race (Black or African American men are more likely to develop PCa²¹). The models were fitted using generalized linear modeling with a binomial distribution and a logit link function, which is commonly used for binary outcomes (presence or absence of csPCa). All continuous variables (eg, age and PSA) were treated as linear predictors, and no interaction terms were included. We trained the models using the data from only 1 protocol and tested in the remaining patients who were biopsy-naïve at time of MRI and received a biopsy post-MRI. The model learned the statistical associations between the predictors and csPCa status, estimating coefficients that quantified their contributions to the log-odds of csPCa presence. Once trained, the logistic regression model was used to predict the probability of csPCa for patients in the test set. The predicted probabilities, representing the likelihood of csPCa, were then used to test the model's performance for patient-level detection of csPCa by GG. We evaluated models with different predictors: (1) age and PSA (clinical factors available before an MRI scan, to establish a baseline performance without any imaging); (2) age and PSAD (available once MRI is performed); (3) age, PSAD, and RSIs (all objective predictors); (4) RSIs and PI-RADS (to see if better than either alone); (5) age, PSAD, RSIs, and PI-RADS (variables available once MRI is performed combined with quantitative [RSIs] and qualitative [PI-RADS] biomarkers); and (6) age, race, PSAD, RSIs, and PI-RADS (to see if adding race to model 5 improved performance).

Statistical Analyses

For patient-level analysis of RSIs, the AUC was calculated from the ROC curve. RSIs AUCs were compared

Table 1. Demographic and Clinical Characteristics of the Patients Included in This Study

Patient characteristics: total study participants (n = 1892)		
Cohorts, No. (%)		
UC San Diego Health	693	(37)
UC San Diego CTIPM	679	(36)
Harvard University's Massachusetts General Hospital	251	(13)
University of Rochester Medical Center	64	(3.4)
UC San Francisco	15	(0.80)
UT Health Sciences Center San Antonio	147	(7.8)
University of Cambridge	43	(2.3)
Clinical parameters		
Age, median (IQR), y	70	(64-75)
PSA, median (SD), ng/mL	6.36	(4.65-9.20)
Prostate volume, median (IQR), mL	51	(36-74)
PSA density, median (IQR), ng/mL ²	0.11	(0.07-0.19)
Biopsy-naïve patients, No. (%)		
Received biopsy before MRI scan	657	(35)
Biopsy-naïve at time of MRI scan	1235	(65)
Subset of biopsy-naïve with a biopsy result within 6 mo after MRI	877	(of 1235)
Biopsy pathology, No. (%)		
Systematic biopsy only	503	(27)
Targeted biopsy only	179	(9.4)
Systematic and targeted biopsy	710	(38)
No biopsy within 6 mo of MRI scan (MRI negative, PSAD ≤0.15)	500	(26)
Prostatectomy pathology in patients who received radical prostatectomy, No. (%)	323	(17)
Highest MRI PI-RADS (v2.1) lesions, No. (%)		
Patients whose highest PI-RADS score in the prostate was 1	636	(34)
Patients whose highest PI-RADS score in the prostate was 2	53	(2.8)
Patients whose highest PI-RADS score in the prostate was 3	263	(14)
Patients whose highest PI-RADS score in the prostate was 4	453	(24)
Patients whose highest PI-RADS score in the prostate was 5	443	(23)
Patients with no PI-RADS scores (research-only scans)	44	(2.3)
Total MRI PI-RADS (v2.1) lesions		
Total No. of PI-RADS lesions	2167	
Total negative (1, 2) PI-RADS lesions, No. (%)	714	(33)
Total positive (3, 4, 5) PI-RADS lesions, No. (%)	1453	(67)
Gleason grade group pathology, No. (%)		
No biopsy within 6 mo of MRI scan	500	(26)
Benign	334	(18)
1	296	(16)
2	367	(19)
3	211	(11)
4	81	(4.3)
5	103	(5.4)
Self-reported race and ethnicity, No. (%)		
White, Hispanic	94	(5.0)
White, non-Hispanic	1228	(65)
White, ethnicity other/unknown	65	(3.4)
Asian	120	(6.3)
Black or African American	117	(6.2)
American Indian/Alaska Native	6	(0.32)
Native Hawaiian or other Pacific Islander	6	(0.32)
Other/unknown	256	(14%)

Abbreviations: CTIPM, Center for Translational Imaging and Precision Medicine; PI-RADS, Prostate Imaging Reporting and Data System; PSAD, PSA density; UC, University of California; UT, University of Texas. Additional details regarding MRI PI-RADS lesions are reported in Supplementary Figure 2 (<https://www.jurology.com>).

with AUCs from minimum ADC and highest PI-RADS category for each patient. Notably, this use of minimum ADC differs from clinical practice, where an expert radiologist identifies a suspicious lesion and then calculates the mean ADC across all or part of that lesion. Using *b*-values of 0, 500, and 1000 s/mm², voxelwise ADC maps (equivalent to vendor-calculated ADC maps^{8,9}) were

computed in MATLAB from the RSI acquisition. PI-RADS reporting was performed per clinical routine by experienced, board-certified, fellowship-trained radiologists. We reviewed medical records to obtain PI-RADS scores for all lesions and histopathology reports. csPCa was determined from best available pathology (biopsy/prostatectomy) and derived from the index lesion with the highest PI-RADS score. As a patient-level analysis, the highest GG detected on each total biopsy/prostatectomy was used to define the patient-level csPCa status. For AUC estimation, we used 10,000 bootstrap resampling to calculate 95% CIs. To compare biomarker AUCs at the patient-level, we computed 2-tailed bootstrap AUC differences. We resampled with replacement the data 10,000 times stratifying by csPCa status and computed AUC differences between biomarkers for each iteration, generating an empirical distribution of these differences. To determine the *P* value, we counted how often the AUC difference was in the opposite direction of the observed trend, effectively testing whether differences could have occurred by chance ($\alpha = .05$). This approach provides a nonparametric, distribution-free method that is well-suited for assessing AUC differences without assumptions of normality. The same method was applied consistently across subset analyses and multivariable models to maintain statistical rigor and comparability.

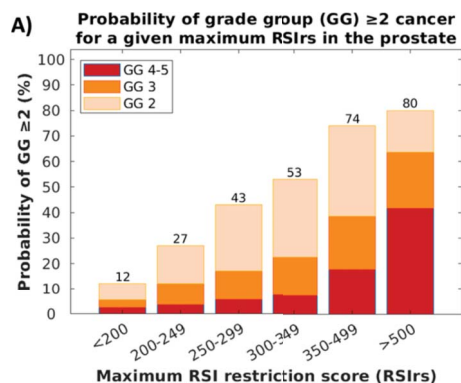
RESULTS

Patient-Level Detection of csPCa

One thousand eight hundred ninety-two patients who underwent prostate MRI at 1 of 7 imaging centers met the criteria for inclusion (Table 1, Supplementary Figures 1 and 2, <https://www.jurology.com>). Data were acquired using 7 distinct acquisition protocols, 2 scanner vendors, 3 scanner models, and 17 MRI scanners (Supplementary Table 2, <https://www.jurology.com>).

Probability of csPCa increased with higher RSIRs. High-grade (GG4-GG5) csPCa was proportionally more common among those with highest RSIRs (Figure 1, Supplementary Figure 3, <https://www.jurology.com>). For RSIRs > 500, there were 80% probability of csPCa found on biopsy and 64% probability of GG ≥ 3 PCa. For RSIRs < 200, patients had 12% probability of csPCa and only 6% probability of GG ≥ 3 PCa. RSIRs and ADC maps are shown for representative patients (Figure 2).

ROC curve analysis demonstrated that RSIRs was superior to ADC and comparable with PI-RADS for patient-level detection of csPCa (Figure 3). Among 877 biopsy-naïve patients with biopsy post-MRI, median AUC for GG ≥ 2 vs non-csPCa was 0.73 (0.69-0.76) for RSIRs, 0.54 (0.50-0.57) for ADC, and 0.75 (0.71-0.78) for PI-RADS. RSIRs outperformed ADC (*P* < .01) and was comparable with PI-RADS (*P* = .31). For GG ≥ 3 vs non-csPCa (ie, excluding GG2), median AUCs were 0.76 (0.72-0.80) for RSIRs, 0.55 (0.50-0.60) for ADC, and 0.79 (0.76-0.82) for PI-RADS (Supplementary Figure 4A, <https://www.jurology.com>). RSIRs



B)

	<200	200-249	250-299	300-349	350-499	>500
No biopsy*	217	72	32	19	10	2
Benign	76	65	32	26	24	7
GG1	51	37	35	19	19	9
GG2	26	36	46	41	72	15
GG3	12	20	20	20	42	20
GG4-5	10	9	10	10	36	38
Total no csPCa	344	174	99	64	53	18
Total csPCa	48	65	76	71	150	73
Total cases	392	239	175	135	203	91

Figure 1. A, Probability of clinically significant prostate cancer (csPCa) and high-grade csPCa for strata of maximum restriction spectrum imaging (RSI) restriction score (RSIs) values in data from $n = 1235$ biopsy-naïve patients. The upper number in each column is the probability of csPCa. B, Number of patients in each maximum RSIs stratum in the present dataset. *Patients with no biopsy were presumed non-csPCa if they had negative MRI results (expert Prostate Imaging Reporting and Data System interpretation was ≤ 2) and PSA density was ≤ 0.15 (these patients are at minimal risk of csPCa²²). GG indicates grade group.

outperformed ADC ($P < .01$) and was comparable with PI-RADS ($P = .14$). RSIs and PI-RADS showed partial specificity for high-grade csPCa, with higher performance for detection of GG3 to GG5 than for GG2 (Figure 3; Supplementary Figure 4B and Table 3, <https://www.jurology.com>). GG ≥ 2 and GG ≥ 3 vs non-csPCa analyses were repeated using biopsy only as the reference standard (Supplementary Figure 5, <https://www.jurology.com>), and using the 99th and 98th percentiles of RSIs (Supplementary Figure 6, <https://www.jurology.com>). RSIs performed similarly to expert PI-RADS in patients with lesions in the TZ ($P = .90$), those with PZ lesions ($P = .07$), and in patients < 60 years ($P = .12$) and ≥ 60 years ($P = .11$). Subset analyses by race were limited by small sample sizes (Supplementary Table 3 and Figure 7, <https://www.jurology.com>).

Multivariable Integrated Risk

Logistic regression models were used to combine predictor variables. The training set comprised 554 patients (44 research scans excluded because of lack of PI-RADS score), including 232 patients (PI-RADS 1-2 and PSA ≤ 0.15) with no biopsy but presumed

free of csPCa.^{22,23} Models were tested in an independent multi-institution dataset with 664 patients, all biopsy-naïve before MRI and with post-MRI biopsy confirmation of csPCa status (Supplementary Figure 1, <https://www.jurology.com>). The combination of RSIs and PI-RADS outperformed either alone ($P < .01$ and $P = .01$, respectively), and a model of age, PSA, PI-RADS, and RSIs achieved the best discrimination of csPCa, outperforming RSIs alone and PI-RADS alone ($P < .01$; Table 2; Supplementary Figures 8 and 9, <https://www.jurology.com>). Addition of race did not significantly improve performance in the multivariable models.

DISCUSSION

We evaluated RSIs as an objective MRI biomarker for detecting csPCa at the patient-level. ADC typically becomes clinically useful after a radiologist identifies a suspicious lesion, but RSIs assesses the entire prostate automatically and performed comparably with expert PI-RADS for csPCa detection in a large multicenter dataset. Pathologic GG is a major prognostic factor for patients with csPCa: Some GG2 cancers may be safely monitored on active surveillance,²⁴ while GG3 to GG5 cancers (where RSIs performed best) are critical to detect and treat early because of their higher metastatic potential.²⁵ Our analyses stratified by GG reflect the uncertainty among some physicians of whether GG2 are important to find. If you are unsure whether GG2 is important to find in a particular patient, for example, it is worth evaluating how well an approach detects what you want to find (GG ≥ 3) and how often it falsely indicates biopsy is necessary (GG1/benign).

An automated measurement of RSIs can give physicians and patients an objective and reliable estimate of the likelihood of csPCa or higher-grade csPCa. Subspecialist radiologists are often at elite centers that provide care for only a small proportion of patients. A quantitative biomarker could contribute to making accurate prostate MRI accessible to patients who do not receive their care at elite centers. PPV of RSIs is inherently reproducible for a given scan because it is calculated objectively from MRI. Use of RSIs could make prostate MRI more reliable and readily interpretable for physicians and patients. By addressing the variable PPV of PI-RADS and reducing dependence on reader expertise, implementation of objective biomarkers could increase health equity in the PCa diagnostic pathway.

RSIs requires only an RSI-MRI acquisition lasting 2 to 3 minutes (without administration of intravenous contrast) for initial evaluation of patients with elevated PSA, yielding an automated biomarker with performance comparable with expert radiologists' evaluations of a full PI-RADS mpMRI scan. We

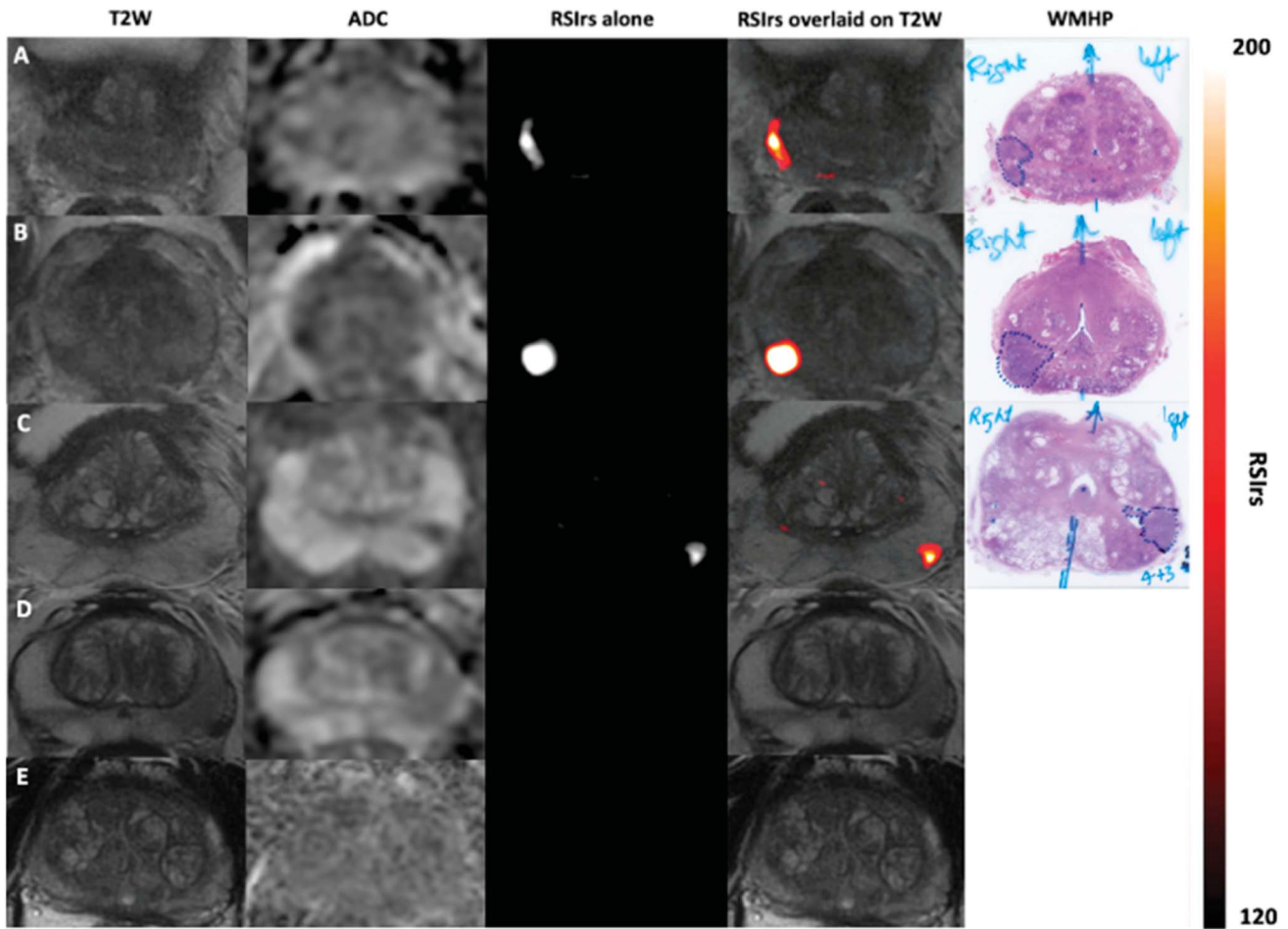


Figure 2. Axial images of T2-weighted (T2W) MRI, conventional apparent diffusion coefficient (ADC), restriction spectrum imaging restriction score (RSIs), and RSIs overlaid on the anatomical T2W images. Arrows are not provided so that the reader can more easily judge the relative conspicuity of the lesions on the various imaging modalities. Patients A, B, and C each had a Prostate Imaging Reporting and Data System 4 lesion in the peripheral zone (right posterolateral for patients A and B, left posterolateral for patient C) that was confirmed as prostate cancer on biopsy. They subsequently underwent prostatectomy (within 6 months of MRI) and were among a small subset of patients in this study who had whole-mount histopathology (WMHP). Tumors for patients A, B, and C were outlined on WMHP by an experienced genitourinary pathologist who was blinded to MRI results. Patient A had Gleason 4 + 4 cancer, while patients B and C had Gleason 4 + 3 cancer. All 3 patients had high maximum RSIs (>300) corresponding to the location of prostate cancer on WMHP. Patients D and E each had a Prostate Imaging Reporting and Data System 5 lesion (D: left lateral peripheral zone; E: right anterior transition zone) assigned by an experienced prostate radiologist during routine care but had low maximum RSIs values (<200). They both subsequently underwent systematic and MRI-targeted transperineal biopsies (within 6 months of MRI) that showed no cancer. Patient D: At 2 years of follow-up, the patient underwent another biopsy, which was, again, negative for cancer. Patient E: At 5 years of follow-up, the patient underwent a simple prostatectomy for benign prostatic hyperplasia; there was no cancer on histopathology.

showed that RSI acquisitions are compatible with standard clinical scanners and can easily be integrated across different vendors and centers. Integration of RSI requires (1) installing the RSI acquisition protocol on the scanner by saving the protocol files on the scanner and (2) calculation of RSIs by installing a software on any basic personal computer.

Beyond the rapid protocol of RSIs, there are a few ways RSIs might be considered for adoption into clinical practice. RSIs could establish a floor for performance of csPCa detection regardless of available radiology expertise. Inexperienced centers currently not offering prostate mpMRI could use

maximum RSIs to increase confidence that results are reasonable. Expert and nonexpert centers could use maximum RSIs to refine reports to indicate the likelihood of high-grade csPCa instead of only high/low possibility of any $GG \geq 2$ cancer. For radiologists and referring physicians alike, a very low RSIs maximum could provide additional reassurance that an MRI examination is nonsuspicious, whereas a very high RSIs maximum might prompt closer scrutiny of the images to ensure nothing has been overlooked.

We focused this study on patient-level csPCa detection. Another important role of MRI is tumor localization for targeted biopsy and radiotherapy

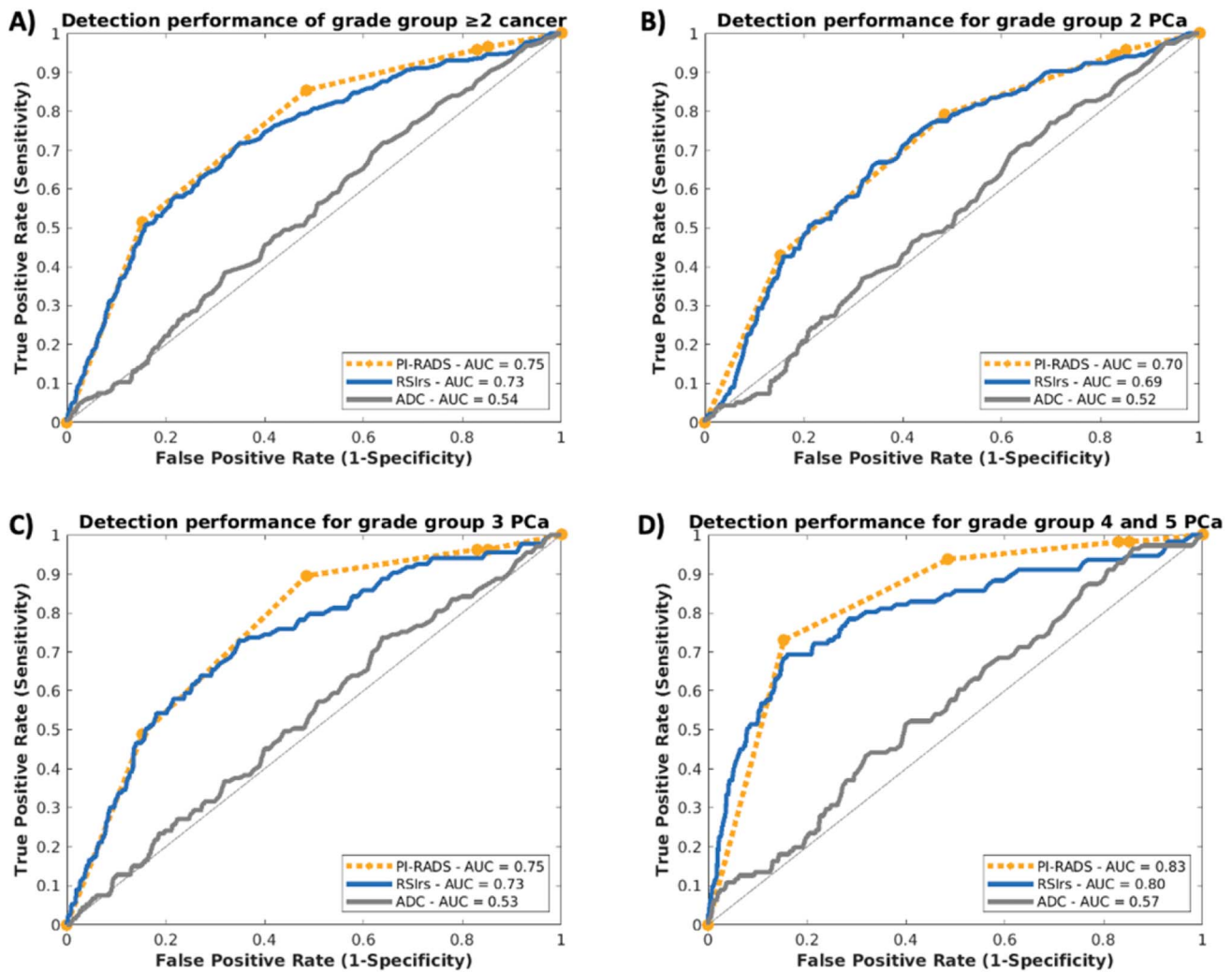


Figure 3. ROC curves by grade group for patient-level detection of prostate cancer (PCa) using restriction spectrum imaging restriction score (RSIrs), Prostate Imaging Reporting and Data System (PI-RADS), and apparent diffusion coefficient (ADC). Patients were included if they were biopsy-naïve at time of MRI and underwent biopsy after MRI. Yellow circles correspond to PI-RADS thresholds. A, AUCs for discrimination of grade group ≥ 2 PCa vs no PCa ($n = 877$). B, AUCs for grade group 2 PCa detection vs no PCa ($n = 633$). C, AUCs for grade group 3 PCa detection vs no csPCa ($n = 531$). D, AUCs for grade group 4 to 5 PCa detection vs no PCa ($n = 509$). RSIrs was superior to ADC in detection of grade group ≥ 2 , 2, 3, and 4 to 5 PCa ($P < .01$). AUCs with 95% CIs and P values are reported in Supplementary Table 3 (<https://www.jurology.com>).

planning.²⁶ Radiologist-defined lesion segmentations were not available to perform lesion-level analysis of this large dataset. The commercial software our centers use to delineate biopsy targets does not permit exporting the segmentations and automatically deletes them to make room for future studies. In any event, expert-defined lesions are subjectively identified, thus undermining the primary goal of the study to consider approaches independent of radiologist expertise. Previous work, though, has shown that RSIrs maps are useful for localization of csPCa, with a strong correlation between RSI and csPCa on whole-mount histopathology. RSIrs maps reflect the location of csPCa and make it more apparent to non-experts.¹⁰ A prospective study showed that radiation oncologists' ability to delineate radiologist-expert-

defined, biopsy-confirmed PI-RADS lesions on MRI was more accurate using RSIrs maps vs conventional MRI alone.

Automated and quantitative MRI approaches may help alleviate the growing shortage of expert radiologists relative to an anticipated surge in PCa diagnoses.²⁷ Other MRI biomarkers have also shown potential clinical utility in previous studies.²⁸ To our knowledge, this study is the largest and most comprehensive validation of a quantitative MRI biomarker for patient-level csPCa detection. Ongoing next steps include analyses with whole-mount histopathology data to evaluate the location and extent of tumors using RSIrs, and evaluating radiomic and deep-learning AI tools that incorporate RSIrs to further enhance detection performance. A patient-level MRI

Table 2. Results From the Multivariable Logistic Regression Models for Combinations of Restriction Spectrum Imaging Restriction Score With Clinical and Imaging Parameters for Discrimination of Clinically Significant Prostate Cancer (Grade Group ≥ 2)

AUCs for csPCa discrimination using multivariable models			
PCa test group	RSIrs	PI-RADS	ADC
(A) GG ≥ 2 (n = 664)	0.72 (0.68-0.76)	0.74 (0.70-0.77)	0.54 (0.50-0.59)
(B) GG2 (n = 500)	0.69 (0.64-0.74)	0.69 (0.64-0.73)	0.53 (0.50-0.58)
(C) GG3 (n = 409)	0.72 (0.66-0.78)	0.74 (0.69-0.79)	0.53 (0.50-0.60)
(D) GG4-GG5 (n = 393)	0.80 (0.73-0.86)	0.85 (0.80-0.89)	0.58 (0.51-0.65)
PCa test group	RSIrs, PI-RADS ^a	PSA, age	PSAD, age
(A) GG ≥ 2 (n = 664)	0.77 (0.73-0.81)	0.62 (0.56-0.66)	0.68 (0.64-0.72)
(B) GG2 (n = 500)	0.73 (0.68-0.77)	0.53 (0.50-0.58)	0.63 (0.58-0.68)
(C) GG3 (n = 409)	0.78 (0.72-0.83)	0.66 (0.57-0.72)	0.67 (0.60-0.73)
(D) GG4-GG5 (n = 393)	0.87 (0.82-0.92)	0.78 (0.70-0.83)	0.81 (0.75-0.86)
PCa test group	PSAD, age, RSIrs	PSAD, age, RSIrs, PI-RADS ^a	PSAD, age, race, RSIrs, PI-RADS ^a
(A) GG ≥ 2 (n = 664)	0.74 (0.70-0.77)	0.79 (0.74-0.82)	0.79 (0.74-0.82)
(B) GG2 (n = 500)	0.69 (0.64-0.74)	0.74 (0.69-0.78)	0.75 (0.69-0.78)
(C) GG3 (n = 409)	0.73 (0.67-0.79)	0.78 (0.72-0.83)	0.78 (0.72-0.83)
(D) GG4-GG5 (n = 393)	0.86 (0.81-0.91)	0.90 (0.85-0.94)	0.90 (0.85-0.94)

Abbreviations: ADC, apparent diffusion coefficient; csPCa, clinically significant prostate cancer; GG, grade group; PCa, prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System; PSAD, PSA density; RSIrs, restriction spectrum imaging restriction score.

PCa test group A, Independent testing in all biopsy-naïve patients at time of MRI with biopsy-confirmed diagnosis who were not used for training; comparison is csPCa vs no csPCa (benign or GG1). Group B, GG2 vs non-csPCa: subset of independent testing dataset with either GG2 csPCa or no csPCa. Group C, GG3 vs non-csPCa: subset of independent testing dataset with either GG3 csPCa or no csPCa. Group D, GG4 to GG5 vs no csPCa: subset of independent testing dataset with GG4 and GG5 csPCa, or no csPCa. 95% CIs were calculated from 10,000-bootstraping stratified by csPCa.

^a Performance in predictor groups was significantly better ($P < .05$) than that of RSIrs alone.

biomarker could also be directly compared with and/or integrated with other biomarkers into a combined, objective risk assessment or sequential pathway. We have demonstrated that concept here by combining RSIrs with PSAD. Future work should investigate other PSA-derived or genomic biomarkers, some of which have a very high reported negative predictive value.²⁹

Our study has some limitations, including a lack of central radiology and pathology review. Biopsy techniques are prone to sampling error and represent an imperfect gold standard. Nonetheless, most patients here underwent both systematic and targeted biopsy, which is the current clinical standard and captures most csPCa.³⁰ Consistent with clinical guidelines, patients with nonsuspicious prostate MRI typically

did not undergo biopsy, raising the possibility of false negatives on PI-RADS, although the risk of this is low.¹³ In addition, patients with hip implants were excluded from this study; the effect of metal artifact on RSIrs is the subject of ongoing research.

CONCLUSIONS

In heterogenous multicenter data, RSIrs proved to be a quantitative imaging biomarker that performs comparably with expert-defined PI-RADS for patient-level detection of csPCa. With only 2 to 3 minutes of scan time on standard clinical MRI platforms, RSIrs gives objective estimates of probability of csPCa, addressing the current clinical challenge of unreliable PPV with PI-RADS.

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EDITORIAL COMMENTS

We read with great eagerness this multicenter study, in which the authors evaluated the use of restriction spectrum imaging restriction score (RSIRs) for detection of clinically significant prostate cancer (csPCa).¹ RSIRs is a biophysical metric obtained from diffusion-weighted MRI and has been proposed as an objective biomarker for csPCA.² Rojo Domingo and colleagues clearly demonstrate RSIRs to be a remarkable tool for the detection of csPCA, eliminating the significant variation in positive predictive value for which the Prostate Imaging Reporting and Data System (PI-RADS) is critiqued.³

The advantages of RSIRs identified by the authors are multifold. In contrast to the aforementioned diagnostic yield variability of the PI-RADS system, RSIRs is readily accessible and does not require a specialized radiologist, instead relying on a quantitative biomarker that highlights the likelihood of csPCA on diffusion-weighted MRI. Not only does this ease reliance and burden on radiologists, but it also could increase access to care with increased throughput of prostate MRI interpretation, especially if implemented in conjunction with biparametric MRI protocols, which decrease imaging time while preserving diffusion-weighted MRI

sequences needed for RSIRs.⁴ The authors indicate that, although RSIRs performed well in identifying grade group (GG) 3 to GG5 cases of prostate cancer, the biomarker demonstrated lower specificity in detecting GG2 disease, comparable with PI-RADS.

In this study, RSIRs outperformed quantitative apparent diffusion coefficients and was comparable in accuracy to PI-RADS, and when used in tandem, RSIRs and PI-RADS outperformed either metric alone. Interestingly, the authors found that combining the PI-RADS system, RSIRs, and patient predictors, such as age or PSA density, outperformed the other models. This highlights the importance of integrative and patient-personalized

approaches to diagnosing and risk-stratifying prostate cancer.

RSIRs, when used in conjunction with other relevant clinical features, is a promising biomarker that may increase accurate csPCa diagnoses while reducing unnecessary biopsies, if integrated into the workflow of prostate imaging interpretation.

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Prostate MRI and the Prostate Imaging Reporting and Data System have changed the way we diagnose and manage prostate cancer. Nonetheless, shortcomings in negative and positive predictive value alike have been described; although some of these issues rest with imaging quality, many are likely attributable to suboptimal interreader reliability and, frankly, human error. The rapid expansion of prostate MRI into community practice is likely to result in larger quality gaps than currently represented in the literature, given that most studies come from experienced, high-volume centers, and groups with poor performance are unlikely to share or publish their data.

We therefore read with great interest the work by Rojo Domingo et al,¹ who report on the restriction spectrum imaging restriction score (RSIRs) as an objective biomarker for clinically significant prostate cancer diagnosis. The performance of RSIRs in conjunction with conventional, readily available measures such as age and PSA density makes a particularly compelling case for the integration of this biomarker into decision-making pathways. An objective, replicable, imaging-based measure of patient risk would greatly benefit the dissemination of quality prostate cancer evaluation

across the spectrum of urology practice—most of which happens outside of academic centers.

With this evidentiary basis established, the larger, looming question remains of RSIRs' implementation into diagnostic strategies and pathways. Some of this could be motivated by further validation of the results of Rojo Domingo et al¹ and results from a larger, prospective study of the impact on clinically meaningful end points of adding RSIRs to existing information during evaluation. Challenges will likely persist as the performance characteristics of composite models reported herein, while an improvement in many regards, are still far from perfect and portend a continued nontrivial rate of overdiagnosis. Ultimately, our experience within the Michigan Urological Surgery Improvement Collaborative suggests that key stakeholder engagement (including urologists, radiologists, and patients alike) and leadership-level buy-in are critical to adoption and implementation at scale.²

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REPLY BY AUTHORS

We sincerely thank the urologists from Wake Forest School of Medicine for their thoughtful and encouraging comments¹ on our study.² We greatly appreciate their recognition of restriction spectrum imaging restriction score (RSIRs) as a promising, objective biomarker for the detection of clinically significant prostate cancer (csPCa), especially when combined with other key clinical variables such as Prostate Imaging Reporting and Data System score, age, and PSA density.

We strongly agree that integrative, personalized approaches are essential for improving prostate cancer diagnosis and risk stratification. Their comments highlight the potential of RSIRs to reduce reader variability and enhance accessibility to high-quality prostate MRI interpretation. ART-Pro³ is an ongoing prospective trial to evaluate whether fast biparametric MRI (bpMRI) protocols combined with RSIRs can facilitate accurate interpretation even by less experienced radiologists. We expect that the combination of bpMRI and RSIRs will help nonexpert radiologists achieve similar performance to expert radiologists using bpMRI or multiparametric MRI for detection of csPCa, while avoiding the drawbacks that are present when

using multiparametric MRI (need for IV contrast and dependence on radiologist expertise).

Regarding detection of grade group 2 disease, we agree that sensitivity can be further improved by incorporating additional features. Future work will explore how to detect adverse pathological features on MRI, such as cribriform glands or intraductal carcinoma, that may indicate higher metastatic risk.

Given our results for patient-level detection of csPCa using RSIRs, we are currently investigating the use of RSIRs maps for lesion localization. In the ReIGNITE⁴ study, we demonstrated that radiation oncologists (ie, nonexpert readers) correctly identify lesion targets for radiotherapy boost much more frequently using RSIRs compared with conventional MRI alone. Building on these findings, we are now validating RSIRs-based lesion localization using whole-mount histopathology data collected at our own institution as the gold standard. We believe RSIRs-based lesions would be particularly helpful for clinical workflows in therapies targeting the visible tumor.

We thank the authors again for their valuable insights and shared enthusiasm for advancing prostate MRI.

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REPLY BY AUTHORS

We thank Drs Lewicki and Borza for their interest in our development of a quantitative MRI biomarker (restriction spectrum imaging restriction score) for diagnosis of clinically significant prostate cancer and for their insightful comments¹ in response to our paper.² Given the enormous body of evidence in support of prostate MRI from large,

well-designed clinical trials, we are alarmed at the low uptake in the United States.³ We share the writers' concern that these excellent studies were performed at mostly elite centers with subspecialist radiologists, conditions that cannot be readily replicated at scale. Thus, even among the minority of US patients who have access to prebiopsy MRI,

there is an unacceptable range of quality and accuracy.

With the restriction spectrum imaging restriction score, we seek to introduce technical improvements to the images and standardization of MRI protocols to democratize high-quality prostate MRI. Lewicki and Borza are correct that widespread implementation is the next challenge, one that can only be met through collaboration of leaders and stakeholders. The writers'

Michigan Urological Surgery Improvement Collaborative is a perfect example of quality improvement at the population level. The Michigan Urological Surgery Improvement Collaborative could be an ideal venue to pilot implementation at scale and to learn how to best close quality gaps, integrate quantitative imaging into clinical workflows, and ensure that patients everywhere have access to established advances in care. We would be happy to work together to make this happen.

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