Prostate Cancer Genomic Classifier Relates More Strongly to Gleason Grade Group Than Prostate Imaging Reporting and Data System Score in Multiparametric Prostate Magnetic Resonance Imaging-ultrasound Fusion Targeted Biopsies

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OBJECTIVE To assess the association between Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) score, the Decipher score, and histologic grade of carcinoma in biopsy tissue among low- to intermediate-risk prostate cancer patients.

METHODS MRI-ultrasound targeted biopsy of regions of interest and concurrent 12-core systematic biopsy was performed on men with Gleason grade group (GG) 1 and 2. We compared Decipher score with PI-RADS scores and biopsy Gleason GG. Subgroup analyses were performed to evaluate patients who underwent radical prostatectomy (RP), and men with Decipher testing from a targeted biopsy core.

RESULTS One hundred two patients with GG1 and GG2 had biopsy Decipher testing. There was no significant difference in the median Decipher scores among the 3 multiparametric magnetic resonance imaging categories. Patients with GG2 vs GG1 in the setting of PI-RADS 4-5 had higher genomic scores ($P = .01$), but no significant difference was noted in patients with PI-RADS ≤ 3. The rate of genomic higher-risk disease on a targeted biopsy from PI-RADS5 was higher in GG2 (75%) vs GG1 (11.1%; $P = .01$). On multivariable logistic regression analysis, the Decipher score ≥ 0.45, (odds ratio (OR) 2.71; $P = .02$), and age (OR 1.11; $P = .004$) remained significant factors associated with Gleason GG2 on biopsy.

CONCLUSION High-risk genomic classification can be seen across all combinations of PI-RADS categories and Gleason GG1 and GG2, confirming a potential utility for Decipher testing in men with low- to favorable intermediate-risk prostate cancer. The Decipher biopsy genomic test related to Gleason GG independent of PI-RADSv2 score. Confirmatory genomic testing for patients undergoing active surveillance appears more valuable than PI-RADSv2 score. UROLOGY 125: 64–72, 2019. © 2018 Elsevier Inc.

The majority of prostate cancer patients diagnosed with prostate cancer have low- or favorable intermediate-risk disease. These patients are at risk for overtreatment as many with low-risk, indolent lesions continue to receive immediate treatment.[1] One of the first steps to reduce overtreatment is to incorporate the use of diagnostic tools that improve a provider's ability to accurately identify low-risk patients. Accurate stratification of patients into risk groups will determine which patients may benefit from active surveillance vs immediate treatment, as well as give providers the confidence to employ the appropriate management strategy.

Active surveillance is a protocol that allows for the postponement of immediate treatment for eligible patients

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while monitoring disease progression.[2] One of the main challenges with active surveillance is accurately distinguishing indolent tumors from aggressive tumors. Although prostate-specific antigen (PSA) levels, Gleason grade group (GG), and multiparametric magnetic resonance imaging (mpMRI) have been used to assess the risk of patients with prostate cancer, there are still shortcomings in accurately stratifying patients. Recently, tissue-based molecular assays such as ProMark, Prolaris, OncotypeDX, and Decipher have improved patient risk stratification.[3]

Decipher is a genomic-based test that measures the expression levels of 22 RNA biomarkers associated with prostate cancer aggressiveness.[4] It has been shown to be independently predictive of metastasis and prostate-cancer specific mortality in the postprostatectomy setting,[5-7] and associated with better clinical decision making regarding adjuvant and salvage radiation therapy.[6,8] Knudsen et al used Decipher testing to show a strong correlation between biopsy specimens and radical prostatectomies, indicating that limited tissue was adequate to perform such a test using transcriptome analysis.[9] Moreover, the prognostic utility of Decipher Genomic Classifier in prostate biopsy specimens was validated,[10,11] and the National Comprehensive Cancer Network included the Decipher molecular assay for prostate biopsies into its clinical practice guidelines in oncology.[12,13] The Decipher biopsy test is now part of the standard-of-care protocol for men diagnosed with early-stage, localized prostate cancer at our institution to help stratify which prostate cancer patients will be suitable candidates for active surveillance or should consider immediate treatment.

A recent study by Radtke et al demonstrated the utility of the Decipher test on mpMRI fusion targeted biopsy in the high-risk prostate cancer setting. There was a strong correlation between MRI-targeted biopsy genomics, genomic signals in radical prostatectomy specimens, and Prostate Imaging Reporting and Data System (PI-RADS) scores, albeit the majority of targeted biopsy cores were from lesions with PI-RADS score 5.[14] The utility of the Decipher biopsy test in magnetic resonance imaging (MRI)-targeted biopsies from men with favorable-risk prostate cancer, however, has not been evaluated. In this context, we sought to assess the association between PI-RADS scores, mpMRI targeted biopsy Decipher score, and pathologic findings among patients with low- to intermediate-risk prostate cancer.

MATERIALS AND METHODS

Patients, mpMRI, and Biopsy Protocols

All men were participants in the Institutional Review Board (IRB) approved Yale Urology Biospecimen and Data repository and were biopsy-naïve, had a prior negative biopsy, or were on active surveillance for prostate cancer. These patients underwent mpMRI including T2-weighted, diffusion-weighted imaging, and dynamic contrast-enhanced on a 3T MRI. As previously reported, all images were read and recorded by genitourinary MRI radiologists at Yale. Lesions were classified according to the PI-RADS version 2.[15,16] From August 2015 to October 2017 and within 3 months of receiving an mpMRI, an MRI-ultrasound fusion targeted biopsy of regions of interest (ROIs), and concurrent 12-core systematic biopsy was performed under local anesthesia using the Artemis biopsy device (Eigen, Grass Valley, CA). Biopsy cores were collected and immediately fixed. Subsequently, all biopsy cores were reviewed in a genitourinary pathology consensus conference and were graded according to the International Society of Urological Pathology recommendations[17] where GG1 equals Gleason score 3 + 3 and GG2 equals Gleason score 3 + 4.

Sample Selection

Patients were selected for analysis if they had low-risk (GG1) or intermediate-risk (GG2) prostate cancer on biopsy. Specimen collection was based on the GenomeDx instructions. The core (targeted or systematic) of at least 1 mm length with the highest Gleason GG (in 91.2% of cases) was selected and punched from the formalin fixed paraffin embedded blocks for Decipher testing. In 7.8% of men, genomic testing was not performed on the core with highest-grade cancer detected on the biopsy session due to low tumor volume in that core. In these cases, a core with a higher volume of lower Gleason grade (ie, genomic testing on GG1 when GG2 was identified elsewhere) was used.

Study Outcomes

The outcome of interest included the association between PI-RADS scores and biopsy Decipher score and biopsy pathologic findings (GG1 and GG2) among a cohort of men with low- to intermediate-risk prostate cancer. Subgroup analyses were performed to evaluate patients who underwent radical prostatectomy during follow-up, men with Decipher genomic testing from a targeted biopsy core (vs nontargeted), and patients with Decipher genomic testing on a biopsy core from GG1 cancer when a GG2 disease was also detected. Adverse pathology was defined as pathologic Gleason 4 + 3 and/or pT3 disease at radical prostatectomy.

Statistical Analysis

Using previously established cut-point scores, Decipher genomic risk categories were defined as low-risk (Decipher score <0.45), intermediate-risk (Decipher score 0.45-0.60), and high-risk (Decipher score >0.60) categories. Variables considered in the analysis included the median Decipher score, the proportion of Decipher risk categories, PI-RADS v2 scores, and biopsy results (GG1 and GG2). Comparisons were made using the Mann-Whitney *U* test or Kruskal-Wallis test for continuous variables and chi-squared test for proportions as determined a priori. A 2-way Analysis of Variance was conducted to examine the effect of biopsy GG and mpMRI risk categories on Decipher score. We performed univariate and subsequent multivariate logistic regression models to study the demographic, clinical, imaging, and genomic factors associated with GG2 on biopsy. We also performed "leave-one-out analysis" excluding the subset of men with a lower grade cancer to determine the accuracy of the findings in the full cohort. All statistical analyses were performed using IBM SPSS Statistics for Windows version 24 (IBM Corp, Armonk, NY). Two-sided *P* values were calculated with α <0.05 considered statistically significant.

RESULTS

Of 291 men with MRI-ultrasound fusion prostate biopsy which showed Gleason GG1−GG2 during the study period, we

identified a cohort of 102 patients (35%) who had genomic testing performed on either targeted or systematic biopsy samples. The median age was 64 years (interquartile range (IQR) 59-70), and the median PSA was 6.09 ng/mL (IQR 4.77-7.91). The majority of patients (56.9%) were on active surveillance prior to the biopsy, while 30 (29.4%) were biopsy-naïve. On mpMRI, the index lesion was scored PI-RADS ≤3 in 21 patients (20.6%), PI-RADS 4 in 55 (53.9%), and PI-RADS 5 in 26 (25.5%). As illustrated in Table 1, there were no significant differences in the median PSA, PSA density, ROI volume, the proportion of African-American men, patients with abnormal digital rectal examination, prior biopsy status, or location of ROI between those with GG1 and GG2 prostate cancer on biopsy. However, the Decipher score and proportion of men with genomic high-risk were significantly higher in men who had GG2 prostate cancer on biopsy ($P = .001$ and $P = .01$, respectively).

Decipher Genomic Testing on Entire Patient Cohort

The median Decipher score was 0.40 (IQR 0.21-0.58) for men with PI-RADS ≤3, 0.41 (IQR 0.29-0.53) for PI-RADS 4, and 0.40 for PI-RADS 5 (IQR 0.26-0.49). There was no significant difference in the median Decipher score among the 3 mpMRI categories within GG1 ($P = .83$, Fig. 1A), GG2 ($P = .89$, Fig. 1A), and the entire group ($P = .78$). There was no statistically significant interaction between the effects of biopsy GG and mpMRI risk categories on Decipher score ($P = .95$). Patients with GG2 vs GG1 in the setting of PI-RADS 4 and PI-RADS 5 had significantly higher genomic scores ($P = .01$ for both; Fig. 1B). No significant association was observed between Decipher genomic risk categories and mpMRI risk categories in the entire group ($P = .63$), among patients with biopsy GG1 ($P = .73$; Fig. 2A), and those with GG2 on biopsy ($P = .71$; Fig. 2B). Although men with biopsy GG2 vs GG1 had greater proportions of genomic higher-risk prostate cancer (Decipher score ≥0.45) in the setting of PI-RADS ≤3, 4, and 5, these associations were not statistically significant (Fig. 2C). We also performed multivariable logistic regression analysis to assess factors associated with GG2 on biopsy (Table 2). Gleason GG2 on biopsy was associated with genomic higher-risk, ie, Decipher score ≥0.45, (OR 2.71, 95% confidence interval (CI) 1.10-6.64.1; $P = .02$), and age (OR 1.11, 95% CI 1.03-1.19; $P = .004$).

Subset of Men Who Underwent Radical Prostatectomy

Fourteen patients (13.6%) underwent radical prostatectomy during follow-up. Table S1 lists the clinical and pathologic features of these patients. Of note, no downgrading was detected at the pathologic assessment of the radical prostatectomy specimen. Adverse pathology at radical prostatectomy was found in 5 patients (35.7%). Figure S1 illustrates the Decipher score, PI-RADS score, and biopsy GG by adverse pathology status. Among

Table 1. Characteristics of the study cohort and subset of targeted biopsy-derived genomics by biopsy result

	Full Cohort			Targeted Biopsy Genomic Subset		
	Grade Group 1 ($n = 62$)	Grade Group 2 ($n = 40$)	*P* Value	Grade Group 1 ($n = 36$)	Grade Group 2 ($n = 29$)	*P* Value
Age, y	63 (59-69)	66.5 (63-72)	**.01**	63 (58.25-70)	66 (62-72)	.19
Race, *n* (%)			.39			.24
White	57 (91.9)	39 (97.5)		33 (91.7)	29 (100)	
African-American	5 (8.1)	1 (2.5)		3 (8.3)	0 (0)	
Abnormal DRE, *n* (%)	17 (27.4)	12 (30)	.65	9 (25)	8 (27.6)	.78
Biopsy status, *n* (%)			.63			.68
Active surveillance	37 (59.7)	21 (52.5)		21 (58.3)	17 (58.6)	
Biopsy-naïve	18 (29)	12 (30)		10 (27.8)	6 (20.7)	
Previous negative biopsy	7 (11.3)	7 (17.5)		5 (13.9)	6 (20.7)	
PSA, ng/mL	5.96 (4.44-7.87)	6.09 (4.44-7.87)	.53	6.17 (4.30-9.67)	5.8 (4.75-7.06)	.66
PSA density, ng/mL/mL	0.11 (0.09-0.15)	0.12 (0.09-0.17)	.55	0.11 (0.08-0.15)	0.11 (0.08-0.17)	.96
PI-RADS score, *n* (%)			.07			.31
≤3	17 (27.4)	4 (10)		9 (25)	3 (10.3)	
4	29 (46.8)	26 (65)		18 (50)	18 (62.1)	
5	16 (25.8)	10 (25)		9 (25)	8 (27.6)	
ROI volume, mm^3	0.57 (0.23-1.25)	0.50 (0.21-1.02)	.41	0.50 (0.20-1.33)	0.70 (0.26-1.30)	.89
ROI location, n (%)			.23			.27
PZ	39 (62.9)	29 (72.5)		22 (61.1)	20 (69)	
TZ	20 (32.3)	10 (25)		11 (30.6)	8 (27.6)	
PZ/TZ	3 (4.8)	0 (0)		3 (8.3)	0 (0)	
AFS	0 (0)	1 (2.5)		0 (0)	1 (3.4)	
Decipher score	0.36 (0.23-0.47)	0.49 (0.36-0.56)	**.001**	0.36 (0.25-0.45)	0.49 (0.36-0.56)	**.004**
Decipher risk category, *n* (%)			**.01**			**.04**
Low risk (<0.45)	42 (67.7)	16 (40)		26 (72.2)	12 (41.4)	
Average risk (0.45-0.60)	16 (25.8)	15 (37.5)		8 (22.2)	11 (37.9)	
High risk (>0.60)	4 (6.5)	9 (22.5)		2 (5.6)	6 (20.7)	

($P < 0.05$).

AFS, anterior fibromuscular stroma; DRE, digital rectal examination; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; PZ, peripheral zone; ROI, region of interest; TZ, transition zone.

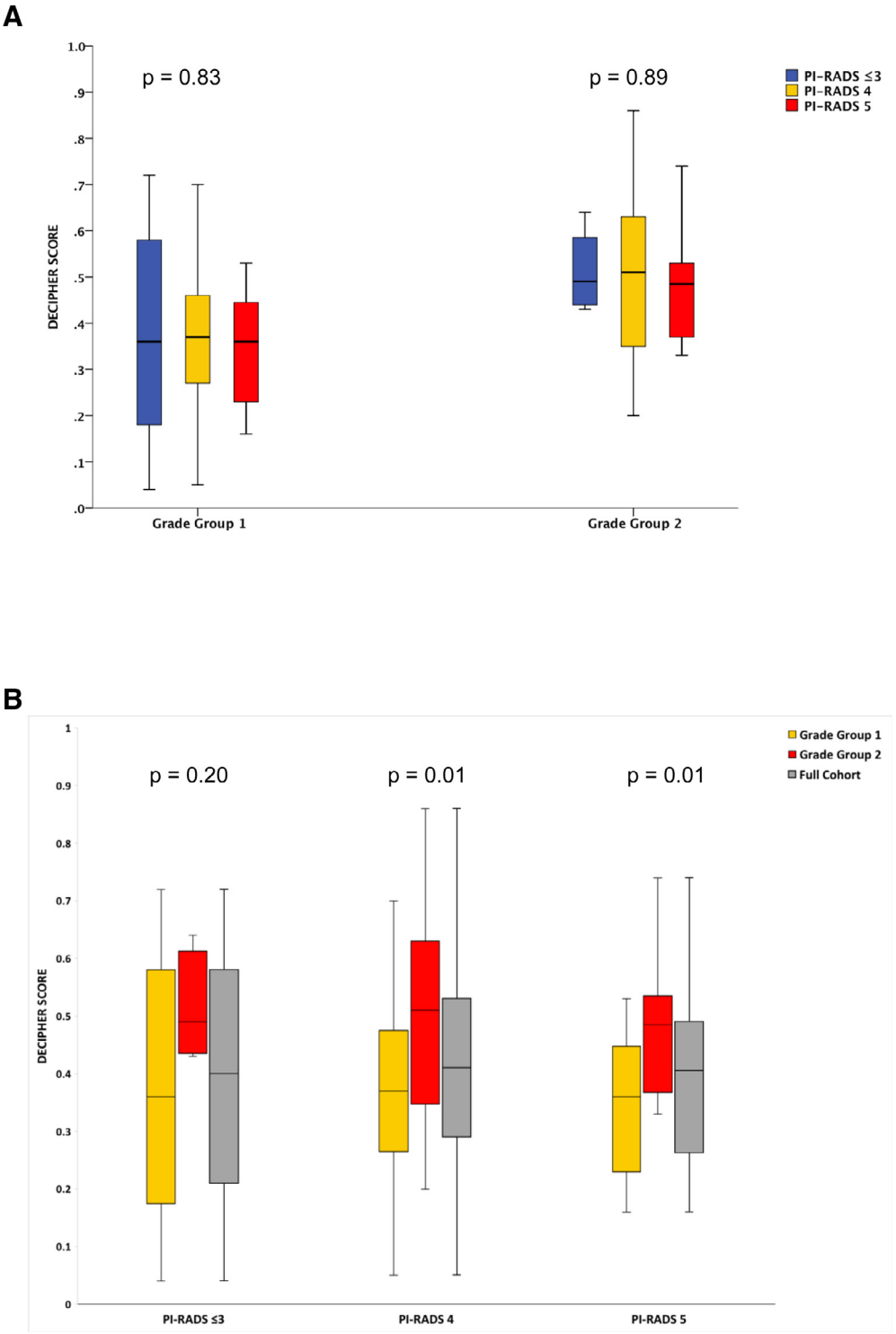


Figure 1. Distribution of Decipher score by MRI PI-RADS scores and biopsy GG. The Decipher score is broken down by (**A**) MRI score (PI-RADS ≤3, 4, or 5) and (**B**) biopsy grade (GG1 or GG2). (Color version available online.)

those with adverse pathology, 4 patients had genomic higher-risk prostate cancer on preoperative biopsy. Notably, 1 patient with PI-RADS 5, biopsy GG1, and genomic low-risk had adverse pathology at radical prostatectomy. In this particular case, the genomic testing was performed on a targeted biopsy core with lower grade cancer (GG1) despite a presence of GG2 prostate cancer on another core from the same PI-RADS 5 lesion.

Subset of Men With Decipher Genomic Testing on Targeted Biopsy Core

Among the full cohort of our study, 66 patients (64%) had genomic testing performed on targeted biopsy cores (Table 1). Similar to the full cohort, a subset of men with genomic testing on targeted biopsy cores harboring GG2 prostate cancer had higher Decipher scores and a greater rate of genomic high-risk (P = .004

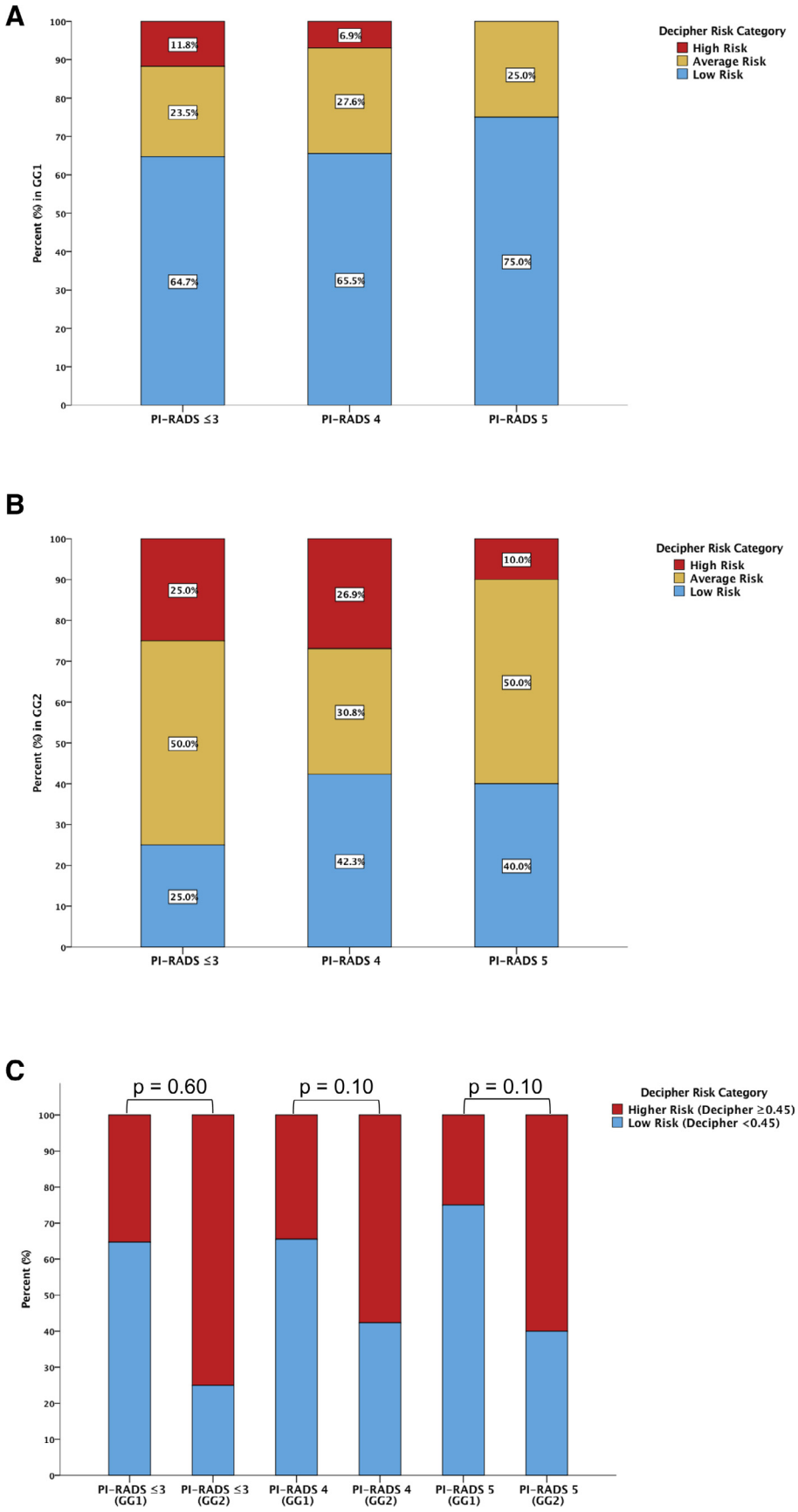


Figure 2. Decipher risk categories by PI-RADS score. Decipher risk categories by mpMRI PI-RADS scores in patients with biopsy GG1 (**A**). Decipher risk categories by mpMRI PI-RADS scores in patients with biopsy GG2 (**B**). Comparing biopsy GG1 with GG2 in the setting of PI-RADS ≤3, PI-RADS 4, or PI-RADS 5, the proportion of Decipher risk, ≥0.45 (average + high risk) vs <0.45 (low risk), is shown (**C**). (Color version available online.)

Table 2. Univariate and multivariate logistic regression examining factors associated with Gleason grade group 2 on biopsy

	Univariate		Multivariate	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	1.13 (1.05-1.21)	<.001	1.11 (1.03-1.19)	**.004**
Race				
White	1.00 (ref.)			
African-American	0.52 (0.09-2.98)	.46		
Abnormal DRE	0.88 (0.37-2.10)	.78		
Biopsy status				
Active surveillance	1.00 (ref.)			
Biopsy-naïve	1.72 (0.70-4.20)	.22		
Previous negative biopsy	1.32 (0.41-4.25)	.64		
PSA	1.11 (0.99-1.24)	.07	1.08 (0.94-1.24)	.23
PSA density (per 0.1 unit)	1.41 (0.79-2.51)	.23		
PI-RADS score, *n* (%)				
≤3	1.00 (ref.)		1.00 (ref.)	
4	3.00 (1.01-8.88)	.04	2.51 (0.74-8.46)	.13
5	2.50 (0.73-8.46)	.14	1.87 (0.45-7.66)	.38
Genomic higher-risk (Decipher score >0.45)	3.08 (1.36-6.96)	.007	2.71 (1.10-6.64)	**.02**

(P < 0.05).

and *P* = .03, respectively). Likewise, patients with GG2 had significantly higher genomic scores on targeted biopsies from PI-RADS 4 and PI-RADS 5 (*P* = .04 and *P* = .01, respectively; Fig. 3A). No association was found between Decipher risk categories and PI-RADS scores among this subset of patients with biopsy GG1 and GG2 (Fig. S2A,B). The rate of genomic higher-risk prostate cancer on a targeted biopsy from PI-RADS 5 was higher in men with biopsy GG2 compared with GG1 (75% in GG2 vs 11.1% in GG1; *P* = .01; Fig. 3B).

Subset of Men with Decipher Genomic Testing on a Biopsy Core With Lower Grade Prostate Cancer

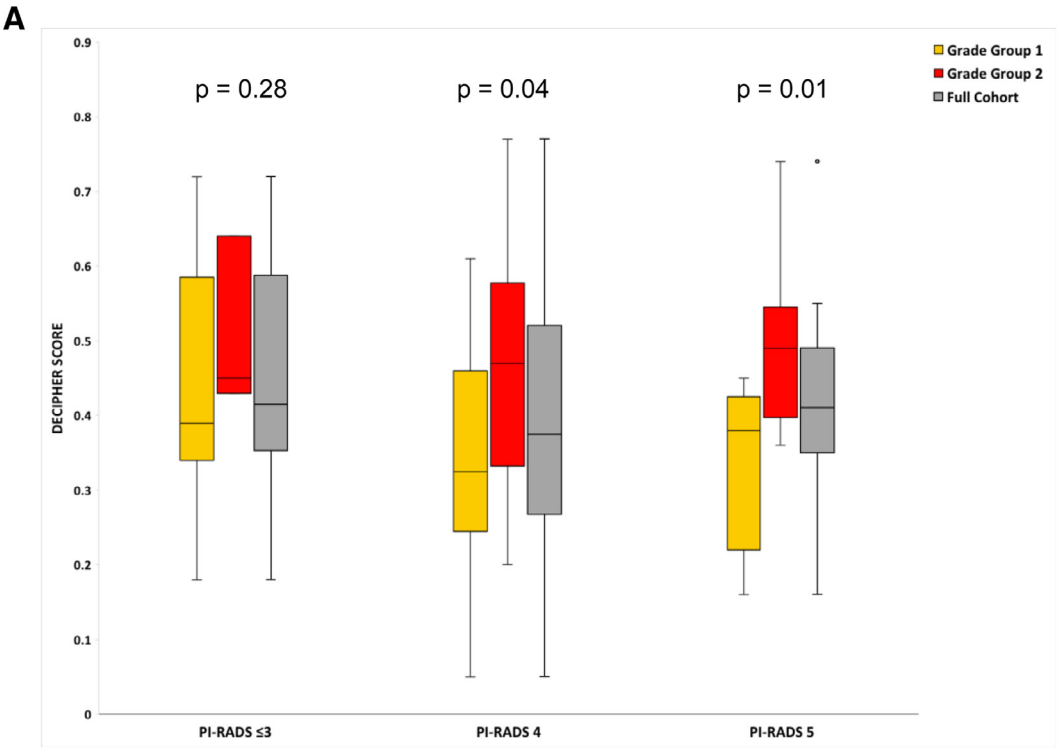
There were no significant differences in the studied variables including the median Decipher score and proportions of genomic risk categories between this subgroup of patients and the remaining study cohort (Table S2). We repeated our analysis after removing this subset of patients from the full study cohort. Similar to the full cohort analysis, patients with GG2 vs GG1 on biopsy and PI-RADS 4 and PI-RADS 5 on mpMRI had significantly higher genomic scores (*P* = .01 and *P* = .03, respectively; Fig. S3A). No association was found between Decipher risk categories and PI-RADS scores on a leave-one-out analysis (Fig. S3B).

DISCUSSION

Men with low- to intermediate-risk prostate cancer would benefit from a better clinical "decision tree" to determine who is appropriate for treatment vs surveillance. To better inform this risk stratification, we examined the association between PI-RADSv2 assessment and the Decipher genomic classifier score in a cohort of men with clinically favorable risk (ie, GG1 and GG2) prostate cancer. We found that the Decipher biopsy test after MRI-ultrasound fusion prostate biopsy relates to Gleason GG more strongly than PI-RADSv2 score in men with low- and intermediate-risk prostate cancer. In our study, we utilized mpMRI-ultrasound fusion targeted biopsies in combination with Decipher testing to describe the gene expression profiles from tissue within the index lesion. This is the first time that Decipher testing in combination with mpMRI-ultrasound fusion targeted biopsy data has been reported.

The Decipher score did not correlate with PI-RADSv2 score in our series, suggesting that mpMRI findings may not be predictive in a low- to intermediate-risk population. Another genomic assay, the Genomic Prostate Score, was found in this population to relate to adverse pathology on prostatectomy and the University of California, Los Angeles (UCLA) MRI grading scale, but not PI-RADSv2,[18] while another assessment using a proprietary 3-point MRI grading scale at University of California, San Francisco (UCSF) also found some correlation between MRI and Genomic Prostate Score score, though there was significant overlap and heterogeneity.[19] Conversely, studies evaluating high-risk prostate cancer demonstrated a strong correlation between MRI-targeted biopsy genomics and PI-RADS scores.[14] Our findings demonstrated a stronger alignment between Gleason and Decipher scores in lesions classified as PI-RADS 5, while a wider distribution was evident in PI-RADS 3 or 4, consistent with the findings of others and potentially calling to question the value of PI-RADSv2 scoring as a prognostic tool in this population, though tissue from the targeted biopsy does appear useful. The active surveillance magnetic resonance imaging study (ASIST) trial, for example, did not find the addition of prostate MRI and magnetic resonance (MR) targeted biopsy to the management of men on active surveillance with GG1 prostate cancer to impact rates of prostate cancer progression on repeat biopsy.[20]

Cancer detected on targeted biopsy from high suspicion lesions (PI-RADS 5) has high concordance between Gleason GG and Decipher score. We found that 75% of men with PI-RADS 5 and GG2 on targeted biopsy had a high Decipher score whereas GG1 disease had a low likelihood of a genomic high-risk cancer. In comparing the full cohort with the targeted biopsy cohort, one would assume that the location of cancer whether from the targeted lesion or elsewhere in the prostate did not influence



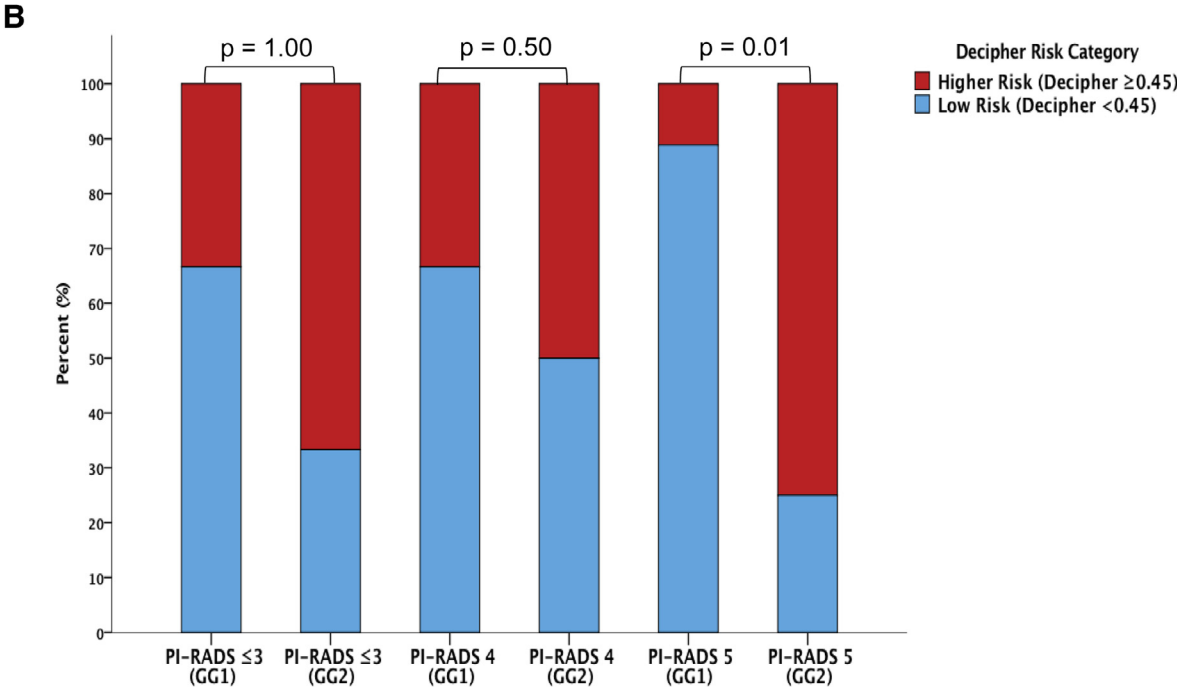


Figure 3. Decipher genomic testing on MRI-ultrasound targeted biopsy cores. Distribution of Decipher score by MRI PI-RADS scores and biopsy GG in subset of men with genomic testing on targeted biopsy core (**A**). Comparing biopsy GG1 with GG2 in the setting of PI-RADS ≤3, PI-RADS 4, and PI-RADS 5, the proportion of Decipher risk, ≥0.45 (average + high risk) vs <0.45 (low risk), is shown (**B**). (Color version available online.)

the correlation between Decipher score and Gleason GG. These findings were similar to Radtke et al who identified a strong correlation between biopsy Decipher score and final pathology in the index lesion. They also noted that sampling was important as there was no correlation between the index lesions and benign regions.[14]

In our targeted biopsy cohort, 25% of men with low-grade (GG1) cancer had high genomic risk disease. This is consistent with the report by Klein et al that 20% of men with low-grade cancer had a higher risk Decipher profile.[21] Conversely, we also found that 25% of men with PI-RADS 5 and GG2 cancer had low Decipher scores, reinforcing the idea that not all intermediate risk cancers are aggressive and require immediate treatment.[22] Follow-up studies are therefore required to determine predictive factors of progression on active surveillance prior to any change in the clinical practice.

There were several limitations to this study. First, we did not have a gold standard, ie, radical prostatectomy specimen analyses for every biopsy performed, since the majority of our patient cohort was on an active surveillance protocol. We attempted to address this by evaluating a cohort of 14 patients for whom whole-mount histopathology was available. Although underpowered to draw conclusions about which factors predict higher risk disease, we did not observe any Gleason downgrading of cases at radical prostatectomy, suggesting that combining MRI, Gleason GG, and Decipher scores in our cohort allowed for appropriate patient selection for definitive therapy. In addition, we had a small sample size for the targeted biopsy data and a larger sample size should be used to validate our findings. Also, there was no information regarding prognosis since this is the initial description of the relation between Decipher, Gleason GG, and MRI. With longer follow-up as part of our ongoing clinical trial, we will be able to determine which factors predict progression in our favorable-risk prostate cancer patient cohort. Additionally, although the use of molecular testing can improve patient stratification, biologic heterogeneity still remains a challenge even with targeted MRI sampling. As other institutions' data mature, we hope to verify our findings across multiple institutional sites before modifying active surveillance protocols since this study lacks external validation.

CONCLUSION

High-risk genomic classification can be seen across all combinations of PI-RADS categories and Gleason GG 1 and 2, confirming a potential utility for Decipher testing in all men with low- to favorable intermediate-risk prostate cancer. The Decipher biopsy genomic test related to Gleason GG independent of PI-RADSv2 score, which may be beneficial when incorporating this genomic marker into a nomogram or a clinical decision-making model. Confirmatory genomic testing for patients undergoing active surveillance appears more predictive than PI-RADSv2 score. Future studies are warranted to determine how these correlate with longitudinal clinical outcomes.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urology.2018.12.001.

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