Practice-Level Variation in the Decision to Biopsy Prostate Imaging-Reporting and Data System 3 Lesions in Favorable-Risk Prostate Cancer Patients

Derek Versalle, Ji Qi, Sabrina L. Noyes, Andrew Moriarity, Arvin George, Michael L. Cher, and Brian R. Lane, for the Michigan Urological Surgery Improvement Collaborative

OBJECTIVE To examine practice-level variation in the management of magnetic resonance imaging (MRI) Prostate Imaging-Reporting and Data System (PI-RADS) 3 lesions in men with favorable-risk prostate cancer (FRPC) considering or on active surveillance (AS).

PATIENTS AND METHODS We reviewed the Michigan Urological Surgery Improvement Collaborative registry for FRPC men (GG1 and low-volume GG2) undergoing MRI from January 2013 to March 2020. The primary outcome was to assess practice-level variation in time from MRI to biopsy and MRI to treatment for PI-RADS 3 lesions. Both MRIs obtained after the diagnostic biopsy and while on AS were included. The Kaplan-Meier method was used to estimate biopsy-free survival for time from MRI to surveillance biopsy and multivariable Cox proportional hazards models identified clinical and demographic factors associated with time obtaining a biopsy after finding PI-RADS 3 lesions.

RESULTS We identified 3172 FRPC men with a MRI, of whom 473 had a PI-RADS 3. There was significant practice-level variation in biopsy rates among patients with PI-RADS 3 MRI results (log-rank test, $P < .001$), with biopsy-free probability at 6 months ranging from 28% to 69% (median: 59%). We were unable to identify factors with significant associations with time to biopsy. Conversely, there was less variation in time from PI-RADS 3 to treatment (log-rank test, $P = .2$), while several clinical factors had statistically-significant associations: age ($P = .018$), Prostate Specific Antigen-Density 0.1-0.2 ($P = .035$), ISUP-GG 2 ($P = .002$), and number of positive cores ($P < .001$), as expected.

CONCLUSION Urology practice, rather than GG or extent of biopsy positivity, is the largest factor affecting the decision for biopsy of PI-RADS 3 lesions in FRPC men considering or on AS. Future work to assist with decision-making and reduce variability is needed. UROLOGY 164: 191–196, 2022.

Active surveillance (AS) is a recommended management strategy for men with low-risk prostate cancer (PCa) and is the preferred approach for very-low risk PCa.[1-6] AS for favorable-intermediate risk PCa is more controversial given the conflicting data regarding long-term outcomes but is increasingly being utilized after considering other clinical factors, such as patient age, life expectancy, and individual preferences. Multiple approaches to the evaluation of patients initially being considered for AS and for continued management of patients on AS have been proposed.[5,7] Despite the wider acceptance of AS in appropriate patients, strong evidence to guide the intensity, interval, and type of surveillance testing (prostate specific antigen [PSA], magnetic resonance imaging [MRI], genomic classifiers, and biopsies) remains to be defined.[7,8]

In recent years, there have been several high-quality studies investigating the utility of MRI in the screening, diagnosis, and staging of men with PCa.[9,10] Supported by the expansion in the data to justify the use of multiparametric MRI and targeted biopsy for men considering

Derek Versalle and Ji Qi contributed equally to the writing of this manuscript.

From the Department of Surgery, Michigan State University College of Human Medicine, Grand Rapids, MI; the Michigan Medicine, Ann Arbor, MI; the Spectrum Health Hospital System, Grand Rapids, MI; the Advanced Radiology Services, Grand Rapids, MI; the Division of Radiology and Biomedical Imaging, Michigan State University College of Human Medicine, Grand Rapids, MI; and the Department of Urology, Karmanos Cancer Center, Wayne State University, Detroit, MI

Address correspondence to: Brian R. Lane, M.D., Ph.D., F.A.C.S., Betz Family Endowed Chair for Cancer Research, Professor of Surgery, Michigan State University College of Human Medicine, Division of Urology, Spectrum Health Medical Group, 145 Michigan Street NE, Suite 5500, Grand Rapids, MI 49503. E-mail: brian.lane@spectrumhealth.org

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or on AS, MRI is becoming increasingly utilized prior to and after the diagnostic biopsy, and prior to surveillance biopsies, for men on AS.[11-13] MRI in this patient population can be beneficial in several regards; some urologists may use the strong negative predictive value of MRI as a method to mitigate the sampling error of the diagnostic biopsy, while others may use surveillance MRI as an opportunity to limit the burden of testing while on AS until new lesions appear and direct future biopsies. With either strategy, the Prostate Imaging-Reporting and Data System (PI-RADS) 3 lesions remain an area of clinical uncertainty.

The purpose of this study was to investigate practice-level variation in the management of PI-RADS 3 lesions in men considering or on AS. Furthermore, we aimed to determine which clinical, demographic, and oncologic factors were associated with the decision made by urologists to biopsy and treat such patients with PI-RADS 3 lesions.

PATIENTS AND METHODS

Patients

The Michigan Urological Surgery Improvement Collaborative (MUSIC) registry is a statewide, physician-led quality improvement consortium.[14] Patient data are entered prospectively by trained medical record data abstractors at respective sites throughout Michigan. Participating practices represent a broad spectrum of academic and community practices, including approximately 90% of the urologists in Michigan. Each MUSIC practice obtained an exemption or approval for collaborative participation from their local institutional review board.

The objective of our study was to assess for practice-level variation in the management of men with favorable risk prostate cancer (FRPC) and PI-RADS 3 MRIs.[15] MUSIC defines FRPC as GG1 of any volume and low-volume GG2 (≤3 cores and ≤50% of an individual core involved with cancer). The primary outcomes were to assess variation in time from MRI demonstrating the PI-RADS 3 lesion to (1) biopsy and (2) treatment. Men that did not have a biopsy or remained free of treatment were censored at the date of their last follow up. Secondary objective was to assess for treatment free survival for men with FRPC stratified by PI-RADS score (0-2, 3, 4, and 5).

We identified all men in the MUSIC registry with FRPC and a MRI after the date of diagnosis between January 2013 and March 2020. MRI performed before the patient's first prostate biopsy, after prior negative prostate biopsy, after prior biopsy with pre-malignant findings (eg, atypical small acinar proliferation, atypia, multifocal high-grade prostatic intraepithelial neoplasia), and MRI performed for unknown reasons were all excluded. Additionally, men that had treatment such as RT or ADT prior to the index MRI were excluded as well (such as radiorecurrent PCa undergoing MRI).

Predictors and Data Analysis

Clinical, demographic, and oncological characteristics of patients were compared by PI-RADS score using Chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous measures. Among patients with PI-RADS 3 at MRI, practice-level variation on time to biopsy and treatment following MRI were graphed via the Kaplan-Meier method and curves were compared with the log-rank test. Only practices with >10 PI-RADS 3 MRI were included in the practice-level variation analysis. We fit separate multivariable Cox proportional hazards models to identify factors associated with the time to biopsy and treatment among all patients with PI-RADS 3 MRIs. The model included both patient-level factors as predictors, as well as random intercepts for practices/hospitals to account for within-center correlation. For the secondary objective, the log-rank test was used to assess for differences in treatment-free survival stratified by PI-RADS score. All the statistical analyses were performed in SAS 9.4, and statistical significance was set at 0.05.

RESULTS

Demographics

A total of 3172 men with FRPC from 34 MUSIC practices underwent MRI after the diagnostic biopsy. Median time between diagnosis and MRI was 6.0 months (interquartile range: 2.8-18.7 months). Patient and pathologic factors for all these patients, and according to resulting PI-RADS scores, are indicated in Table 1. Patients with higher PIRADS scores on average were older, with smaller prostate volumes, and higher PSA, PSA-Density (PSA-D), higher number of positive cores, and greater proportion having GG2 PCa (P <.001 for each).

Practice-Level Variation

Among the 473 patients with PI-RADS 3 MRI, there was significant variation in time to subsequent biopsy across practices (Fig. 1A). Since June 2016, 244 of the 473 PIRADS 3 patients had a post-MRI biopsy. Of these biopsies, 182 were fusion biopsies (75%) and 62 were standard biopsies (25%). By 6 months, the biopsy-free probability ranged from 28% to 69% (median = 59%) for contributing practices. There was less variation observed with respect to time to receiving treatment after MRI across practices (Fig. 1B, P = .21). By 6 months, the treatment-free probability in participating practices ranged from 64% to 100% (median: 77%). In all MUSIC practices, over half of men with PI-RADS 3 lesions remained free of treatment for greater than 18 months from the time of the PI-RADS 3 MRI (Fig. 1B).

Factors Associated With Biopsy and/or Treatment

To assess the factors that were associated with time to biopsy, multivariable models were constructed (Table 2). The following factors were not found to be significant predictors of time to biopsy: age, race, family history, PSA, prostate volume, PSA-D, ISUP GG, number of positive cores, clinical stage (T1 vs T2/T3), or clinical setting (consideration of AS vs ongoing AS).

In contrast, several of these clinical factors were associated with time to treatment after PI-RADS 3 MRI (Table 2). The factors having a statistically significant association with treatment included age (HR: 0.97 per 1 additional year, 95% CI: 0.94, 0.99), higher PSA-D (PSA-D 0.1-0.2 HR: 1.78, 95% CI: 1.04, 3.05 vs PSA-D <0.1), GG 2 (HR: 2.15, 95% CI: 1.31, 3.51 vs GG 1), and number of positive cores (HR: 1.33 per additional core, 95% CI: 1.18, 1.50).

Treatment Free Survival by PI-RADS Score

PI-RADS score was strongly associated with the selection and time to treatment for men with FRPC when considering all PI-RADS (Fig. 2, P <.001). By 12 months following MRI, the

Table 1. Characteristics of patients with favorable risk PCa at the time of MRI according to PI-RADS score

	All Patients	PI-RADS 0-2	PI-RADS 3	PI-RADS 4-5	*P*-value
No. patients	3172	1483	473	1216	
Age	64.6 (7.4)	64.0 (7.5)	64.5 (7.1)	65.4 (7.2)	<.001
Race					.012
White	2578 (81.3%)	1185 (79.9%)	377 (79.7%)	1016 (83.6%)	
AA	311 (9.8%)	158 (10.7%)	56 (11.8%)	97 (8.0%)	
Other	76 (2.4%)	45 (3.0%)	13 (2.7%)	18 (1.5%)	
Unknown	207 (6.5%)	95 (6.4%)	27 (5.7%)	85 (7.0%)	
Family history of PCa					.644
Yes	984 (31.0%)	453 (30.5%)	158 (33.4%)	373 (30.7%)	
No	2043 (64.4%)	963 (64.9%)	290 (61.3%)	790 (65.0%)	
Unknown	145 (4.6%)	67 (4.5%)	25 (5.3%)	53 (4.4%)	
Clinical T stage					.233
T1	2831 (89.2%)	1324 (89.3%)	430 (90.9%)	1077 (88.6%)	
T2/3	305 (9.6%)	137 (9.2%)	39 (8.2%)	129 (10.6%)	
Tx	36 (1.1%)	22 (1.5%)	4 (0.8%)	10 (0.8%)	
Prostate volume	52.5 (31.4)	55.0 (35.0)	53.1 (30.2)	49.2 (26.7)	<.001
PSA	6.3 (4.6)	6.0 (4.2)	6.0 (3.2)	6.7 (5.4)	<.001
PSA density					<.001
<=0.1	1215 (38.6%)	665 (45.4%)	183 (39.1%)	367 (30.3%)	
0.1-0.2	1381 (43.9%)	588 (40.2%)	212 (45.3%)	581 (47.9%)	
>0.2	549 (17.5%)	211 (14.4%)	73 (15.6%)	265 (21.8%)	
Biopsy grade group					<.001
3+3	2636 (83.1%)	1270 (85.6%)	401 (84.8%)	965 (79.4%)	
3+4	536 (16.9%)	213 (14.4%)	72 (15.2%)	251 (20.6%)	
No. positive cores	2.1 (1.5)	1.9 (1.5)	2.0 (1.5)	2.4 (1.6)	<.001

MRI, magnetic resonance imaging; PCa, prostate cancer; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, prostate specific antigen.
Data are presented as Mean (SD) or N (%).

estimated probability of patients undergoing treatment was 14% for PI-RADS 1/2, 27% for PI-RADS 3, 49% for PI-RADS 4, and 73% for PI-RADS 5 lesions.

DISCUSSION

The management for men with PI-RADS 3 MRI while considering or on AS remains a point of uncertainty. For patients with indeterminate MRI findings (PI-RADS 3), we found considerable practice-level variation in management of such lesions with regards to time to next biopsy and time to treatment. Additionally, we did not identify clinical, demographic, or oncological factors associated with the time to next biopsy for men with PI-RADS 3 lesions. Interestingly, despite this variation, 73% of patients remained free of treatment at 12 months with notably less practice-level variation seen.

Professional societies and PCa guidelines vary considerably in their recommendations for and performance of AS.[16-18] Although all rely on serial PSA testing, clinical

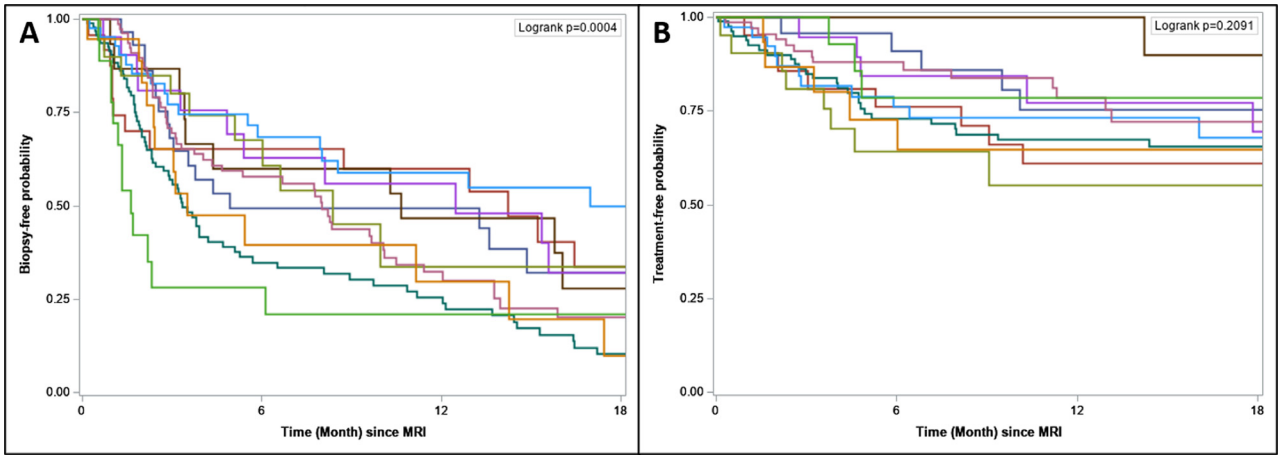

Figure 1. Practice-level variation in time to biopsy (**A**) and treatment (**B**) in response to PI-RADS 3 MRI in favorable-risk patients need treatment graph. MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging-Reporting and Data System. (Color version available online.)

Table 2. Multivariate analysis of factors associated with time to prostate biopsy and time to treatment after PI-RADS 3 MRI in patients with PCa

	Time to Biopsy			Time to Treatment		
Parameter	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (per 1 additional year)	1.01	(0.99, 1.03)	.407	0.96	(0.94, 0.99)	.013
African American Race (vs White)	1.02	(0.67, 1.53)	.937	0.61	(0.30, 1.25)	.180
Other Race (vs White)	0.83	(0.35, 1.96)	.664	1.99	(0.59, 6.63)	.265
Unknown Race (vs White)	0.61	(0.32, 1.15)	.125	0.94	(0.40, 2.22)	.883
Unknown family history (vs Negative)	0.71	(0.33, 1.56)	.398	0.94	(0.33, 2.68)	.901
Positive family history (vs Negative)	1.32	(1.00, 1.76)	.053	1.24	(0.82, 1.88)	.310
Clinical stage T2/T3 (vs T1)	0.57	(0.29, 1.15)	.119	1.32	(0.56, 3.13)	.524
Log.PSA	1.17	(0.80, 1.71)	.428	0.80	(0.43, 1.47)	.468
PSA density 0.1 to 0.2 (vs <0.1)	0.95	(0.70, 1.29)	.736	1.73	(1.01, 2.97)	.044
PSA density >0.2 (vs <0.1)	0.71	(0.43, 1.16)	.169	1.51	(0.70, 3.24)	.292
Grade Group 2 (vs 1)	0.85	(0.56, 1.29)	.452	2.24	(1.37, 3.65)	.001
Positive cores (per additional core)	1.04	(0.93, 1.16)	.477	1.34	(1.19, 1.50)	<.001
Ongoing AS (vs Initial Evaluation)	0.91	(0.69, 1.20)	.508	0.78	(0.51, 1.18)	.237

AS, active surveillance.

evaluations, and additional cancer assessments, such as repeat biopsy, MRI, and genomic analysis of prostate tissue, the recommended uses and timing of these evaluations are not clearly stated.[16,19] MRI is a commonly performed component of the AS pathways employed by many urology practices, offered to both patients with FRPC to assess appropriateness for AS and to monitor for growth or development of new clinically significant PCa while on AS.[1,2,5,6,11,20] While PI-RADS ≤2 may provide assurance in the absence of clinically significant disease and PI-RADS ≥4 may prompt additional evaluation and a prostate biopsy, the management of men with PI-RADS 3 group remains the most nebulous, as these patients have been assigned an indeterminate result.[21] This clinical uncertainty was seen in our multi-institutional analysis given the wide range in practice patterns in the probability of undergoing a prostate biopsy within 6 months of a PI-RADS 3 lesion. Interestingly, while younger age, higher PSA, higher PSA-D, more positive biopsy cores, and GG2 (vs GG1), were all significantly associated with treatment, none of these factors were associated with the decision to biopsy a PI-RADS 3 lesion. The main determinant of

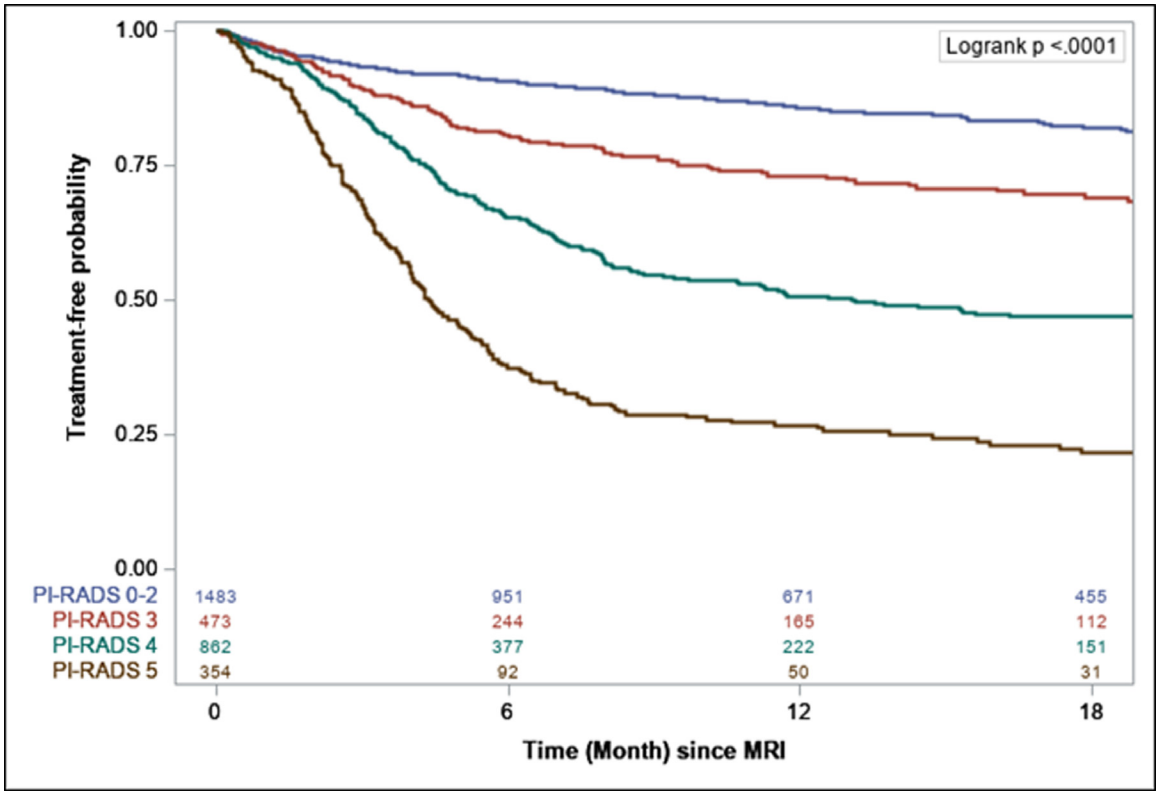

Figure 2. Time to treatment following prostate MRI according to PI-RADS score. MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging-Reporting and Data System. (Color version available online.)

whether and when a biopsy was performed was the individual urology practice, which has important implications for the conduct of AS in appropriate PCa patients.

There are several facets to consider while considering the high degree of variability in the management of PI-RADS 3 lesions. First, cancer-detection rates for PI-RADS 3 are low. In a recent meta-analysis, high-grade PCa, defined as GG3 or higher, has been detected in 6%, 16%, and 43% of PI-RADS 3, 4, and 5 lesions, respectively, in a biopsy-naïve population.[21] For men with PCa on AS, the rates of detection of clinically-significant disease are even lower: 4%, 11%, and 28% for PI-RADS 3, 4, and 5 lesions, respectively.[21] Some clinicians may; therefore, see limited benefit to a repeated biopsy targeting a PI-RADS 3 lesion, when the initial likelihood of finding a GG3 or higher PCa is ~5%. Second, the criteria for AS are broadening to include low volume GG2. Therefore, if a patient in whom AS would still be pursued if low-volume GG2 is present, then repeat biopsy following PI-RADS 3 may be avoidable because even if some low volume GG2 disease were found, management would not be changed. Conversely, if upgrading from GG1 to GG2 may lead a patient to pursue (or a clinician to recommend) treatment rather than continue AS, a urologist may be more likely to biopsy PI-RADS 3 lesions. In this setting, biopsy would be expected to upgrade to GG2 or higher in between one-fifth and one-sixth of patients (and 30%-50% of the PCa's that are detected).[21] It would follow that the endpoint of interest (GG2 or higher vs GG3 or higher) might greatly impact the decision to biopsy, and clinical factors associated with upgrading of PCa at subsequent biopsy or at prostatectomy may be the factors best to use for determining whether to biopsy following an MRI scored as PIRADS 3.[22] Lastly, the decisive management of PI-RADS 3 lesions remains unclear complicated by the lack of standardized practice guidelines. MUSIC conducted an AS panel using modified Delphi methodology last in 2015,[3] finding significant variation in provider opinions on >160 clinical scenarios regarding which patients are appropriate for AS. There are plans to conduct a new AS panel to help provide additional clarity to urologists, given all of the developments and new data regarding MRI and targeted biopsy in this space.

Our study has limitations, including those of any retrospective review of a clinical data registry. The unique infrastructure of MUSIC permits collection of data across a wide range of practices, expanding the applicability of our findings, but also with the associated imperfections of data collection by multiple teams of personnel. Variability in reporting and interpretation of MRI by the multiple radiologists and radiology groups is another limitation. The MUSIC registry began recording standard vs fusion biopsy in June 2016, and complete pathologic data for tracking whether cancer was present in targeted cores, was not routinely available for this cohort. While we view the opportunities within MUSIC as a strength, there are weaknesses compared with more unified analyses of patients receiving care from a single institution or practice.

In the authors' practices, we use biopsy immediately after an MRI with a PI-RADS 3 lesion only sparingly. Until best practices or relevant endpoints are better defined, we recommend the decision to undergo a biopsy following an MRI with a PI-RADS 3 lesion be individualized according to previous biopsy results, oncological parameters, risk tolerance, and patient preference. There is evidence to support either approach, observation vs biopsy of PIRADS 3 lesions, at the present. Further investigation incorporating predictive tools, nomograms, and educational strategies may help provide additional clarity of which patients considering or on AS are most likely to benefit from biopsy of a PI-RADS 3 lesion.

CONCLUSION

There is significant variability in practice patterns regarding the decision to perform a biopsy in men with FRPC and PI-RADS 3 lesions. At the present, the decision for observation vs biopsy for a man with a PIRADS 3 lesion should be individualized. Better delineation of AS pathways and identification of appropriate triggers for biopsy and treatment are important next steps to improve the quality of care for patients when specific guidance and recommendations are unclear, as is currently the case for FRPC patients with PI-RADS 3 lesions.

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