



# Association Between Early Confirmatory Testing and the Adoption of Active Surveillance for Men With Favorable-risk Prostate Cancer

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<b>OBJECTIVE</b>	To examine the relationship between the use and results of early confirmatory testing and persistence on active surveillance (AS).
<b>METHODS</b>	We identified all men in the Michigan Urological Surgery Improvement Collaborative registry diagnosed with favorable-risk prostate cancer from June 2016 to June 2017. We next examined trends in the use of early confirmatory test(s), defined as repeat biopsy, prostate magnetic resonance imaging, or molecular classifiers obtained within 6 months of the initial cancer diagnosis, in patients with favorable-risk prostate cancer. We then compared the proportion of men remaining on AS 6 months after diagnosis according to reassuring vs nonreassuring results, also stratifying by age and Gleason score.
<b>RESULTS</b>	Among 2529 patients, 32.7% underwent early confirmatory testing within 6 months of diagnosis. Its use increased from 25.4% in the second quarter of 2016 to 34.9% in the second quarter of 2017 ( $P = .025$ ). Molecular classifiers were most frequently used (55%), followed by magnetic resonance imaging (34%) and repeat biopsy (11%). Sixty-four percent ( $n = 523$ ) had a reassuring result. Rates of AS were higher for patients with early reassuring results; 82% remained on AS ( $n = 427$ ) compared to 52% ( $n = 157$ ) of those with nonreassuring results and 51% ( $n = 873$ ) with no early confirmatory testing ( $P < .001$ ).
<b>CONCLUSION</b>	Rates of AS are higher among men with early reassuring results, supporting the clinical utility of these tests. Nonetheless, high rates of AS among patients with nonreassuring results underscore the complexity of shared decision-making in this setting. UROLOGY 118: 127–133, 2018. © 2018 Elsevier Inc.

One of the major challenges with initial decision-making for men with newly diagnosed prostate cancer (PCa) is adequate risk stratification. In the Michigan Urological Surgery Improvement Collabora-

tive (MUSIC), efforts to optimize the use of active surveillance (AS) include a roadmap (ie, *The Roadmap for Men with Favorable-Risk Prostate Cancer*) that advocates for the performance of 1 or more confirmatory tests within 6

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months of the diagnosis of favorable-risk PCa.<sup>1</sup> A confirmatory test is an additional evaluation to the initial diagnostic prostate biopsy that aims to better assess disease burden or aggressiveness of the tumor. The rationale for the early confirmatory test is to, as early as possible, address the potential for inadequate risk stratification based on sampling error with the original diagnostic biopsy. This recommendation reflects a position that, if a patient has higher grade or higher volume disease at the time of diagnosis, it is important to appropriately reclassify his risk shortly after the original diagnosis, rather than wait an extended period of time for a repeat surveillance biopsy or other confirmatory testing. Reflecting the diversity of experience, resources, and practice patterns across 44 participating practices, as well as the current absence of strong scientific evidence supporting the clear benefit of any single test, repeat prostate biopsy, multiparametric magnetic resonance imaging (MRI), or tissue-based molecular classifier testing have all been proposed as reasonable confirmatory tests in this clinical setting; MUSIC does not favor one over another.<sup>1</sup> Furthermore, whereas MUSIC encourages early confirmatory testing within 6 months of diagnosis for better risk stratification, for patients remaining on AS, MUSIC advocates for (and the *Roadmap* provides guidance on) reassessment and reclassification of risk according to either a high- or low-intensity surveillance plan.

Although there is support within the collaborative regarding the rationale for early confirmatory testing, it remains unknown whether the use of such tests is increasing across the state in response to these recommendations. Moreover, it is unclear if initial treatment decisions by urologists differ by type or results of confirmatory testing performed, and whether this is consistent across specific patient populations.

In this context, we evaluated rates of early confirmatory testing among patients in Michigan with newly diagnosed favorable-risk PCa. In addition, we examined the association between results of confirmatory testing and the ultimate adoption of AS. We hypothesize that a greater share of patients with reassuring confirmatory test results will remain on AS compared to those with nonreassuring results. By virtue of this approach, our findings help clarify the potential impact of confirmatory testing on adoption of AS.

## METHODS

### Michigan Urological Surgery Improvement Collaborative

Established in 2011 with support from Blue Cross Blue Shield of Michigan (BCBSM), MUSIC is a physician-led quality improvement collaborative that aims to improve quality and decrease costs of PCa and urologic care. Currently, about 90% of urologists in Michigan, at 44 sites across the state, participate in the program. Each participating practice has a trained data abstractor that collects and enters detailed demographic and clinicopathologic data into a web-based registry for patients undergoing a prostate biopsy and

those with newly-diagnosed PCa. The abstractors continue to enter treatment and follow-up data at fixed intervals. In addition, data in the registry are audited regularly to verify accuracy; ad hoc validation studies have also been performed for key data elements including PCa treatments.<sup>2</sup> Collaborative-wide data are available for analysis and quality improvement activities through an electronic clinical registry.

**Study Population.** For this analysis, we identified all men in the MUSIC registry who were newly diagnosed with favorable-risk PCa from June 2016 through June 2017. In MUSIC, we define favorable-risk cancer based on the following grade and volume criteria from the prostate biopsy: (1) any volume Gleason 3 + 3 = 6 disease, or (2) low-volume Gleason 3 + 4 = 7, defined as 1-3 cores positive with no cores of Gleason 3 + 4 with >50% cancer involvement. While the inclusion of patients with low-volume Gleason 3 + 4 is controversial, these patients are included in previously evaluated AS cohorts,<sup>3,4</sup> and it was the consensus of the panel, composed of urologists from across the State of Michigan, that these patients be included as candidates for AS.<sup>5</sup>

**Confirmatory Testing.** Our exposure variable for this analysis is the use of early confirmatory testing. In its *Roadmap*, MUSIC encourages the use of repeat prostate biopsy, MRI, or molecular classifiers for confirmatory testing within 6 months of the original biopsy as part of the consideration process for AS.<sup>1</sup> The *Roadmap* was introduced in December 2016 and widely distributed to MUSIC practices shortly thereafter. Biopsy-based molecular classifier testing includes the Prolaris cell cycle progression score (Myriad Genetics, Salt Lake City, UT), the Decipher genomic classifier (GenomeDx Biosciences, Vancouver, British Columbia, Canada), or the OncotypeDx genomic prostate score (Genomic Health, Redwood City, CA). In the *Roadmap*, and in this analysis, confirmatory test results were classified as either reassuring or nonreassuring, defined by the following criteria: prostate biopsy—if original pathology Gleason 6, upgrading to >Gleason 6; if original pathology low-volume Gleason 3 + 4 = 7, progression to tumor volume or grade that no longer meets criteria for favorable-risk disease; MRI—maximum prostate imaging and reporting data system (PIRADS) v2 of 1 or 2; Prolaris <3% probability of PCa mortality, OncotypeDx >80% freedom from high-grade disease or ≤20% high-grade disease, Decipher <0.45. Although no clinically validated molecular classifier cut-points existed during the time period of this study, these cut-points have been published previously by others and are demarcated on the testing reports provided to patients and physicians.<sup>6-9</sup>

For patients with more than 1 confirmatory tests obtained within 6 months after diagnosis, assignment to an analytic cohort was based on their initial confirmatory test. The final result of confirmatory testing, however, was designated as reassuring or nonreassuring based on the following hierarchy: (1) biopsy result and (2) result of the last

confirmatory test performed within the 6-month “consideration” phase.

**Outcomes.** Our primary outcome measure was persistence on AS. In MUSIC, determination of AS as the primary management strategy is based on explicit documentation by the provider in the medical record. Persistence on AS is determined as those initially on AS, with no definitive treatment occurring within 6 months of the PCa diagnosis. The accuracy of the MUSIC registry for identification of patients on surveillance has been reported in previous validation studies.<sup>2</sup>

**Statistical Analysis.** We first examined both the frequency and results of early confirmatory testing across the entire collaborative. Next, in our primary analysis, we evaluated the proportion of patients remaining on surveillance 6 months after diagnosis according to the results of the confirmatory tests (reassuring vs nonreassuring). We further evaluated these results by the number of reassuring confirmatory tests. Third, we performed subgroup analyses to examine the frequency of surveillance contingent on the results of confirmatory testing based on age (<65 vs ≥65 years at diagnosis) and grade (Gleason score 3 + 3 = 6 vs 3 + 4 = 7) criteria.

We performed chi-square tests, as appropriate, to evaluate statistical significance of the comparisons of interest. We also fit a multivariable regression model to evaluate the association between confirmatory test results (ie, reassuring vs nonreassuring result) and persistence with AS, adjusting for type of confirmatory test, initial Gleason score at diagnosis, pathologic T stage (T1c vs ≥T2a), race, age, and prostate-specific antigen as independent variables. We also accounted for many patients being treated by the same physicians. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) at the 5% significance level. The University of Michigan Institutional Review Board deemed this study exempt from review.

### Sensitivity Analyses

We performed 3 sensitivity analyses to test the robustness of our conclusions. Given that some consider a PIRADS 3 lesion on MRI to be a reassuring confirmatory test, we performed a sensitivity analysis where we classified PIRADS 3 lesions (n = 42) according to this management approach and determined if adoption of AS with a reassuring confirmatory test was different compared to a nonreassuring or no confirmatory test. Second, since preferences for pursuing AS are likely different between patients with initial Gleason 3 + 3 compared to low-volume Gleason 3 + 4 PCa, we separated these 2 cohorts. Third, because MUSIC guidelines include all patients with favorable-risk PCa as candidates for AS, we performed a sensitivity analysis where we classified a “nonreassuring” biopsy as 1, which no longer met “favorable risk” criteria (ie, ≥4 cores of Gleason 3 + 4 cancer), and determined both the share of confirmatory tests that were reassuring and the proportion of patients remaining on AS within 6 months

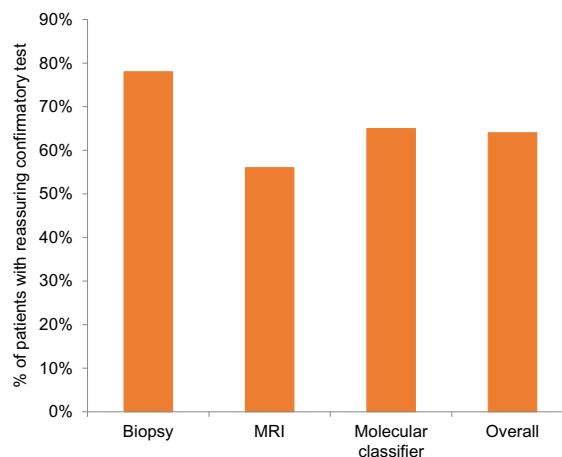
of diagnosis based on biopsy confirmatory test results with this criteria.

## RESULTS

We identified 2529 men diagnosed with favorable-risk PCa from June 2016 through June 2017. Among this group, 826 patients (33%) underwent early confirmatory testing within 6 months of diagnosis. Across the entire MUSIC collaborative, use of early confirmatory testing in patients with favorable-risk PCa increased from 25.4% for men diagnosed in the second quarter of 2016 to 34.9% for those diagnosed in the second quarter of 2017 ( $P = .025$ ) (Supplementary Fig. S1). Molecular classifiers were the most frequently used confirmatory test (55%), followed by MRI (34%) and repeat prostate biopsy (11%).

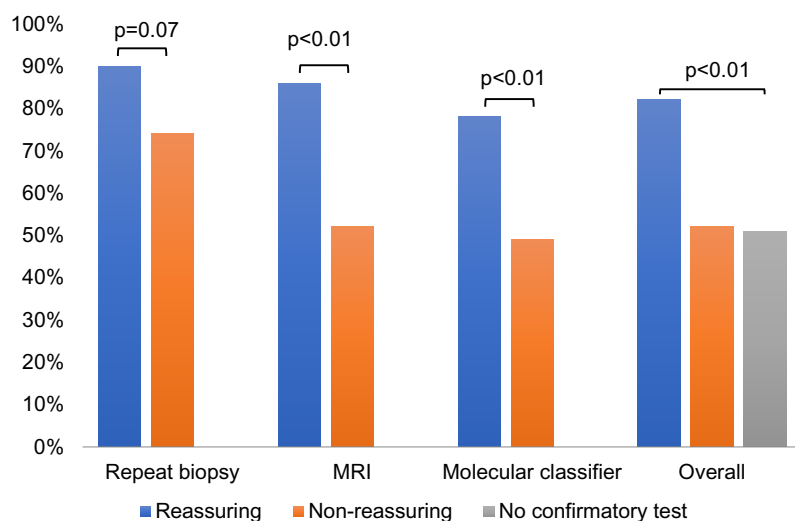
Overall, 64% of patients (n = 523) had a reassuring confirmatory test result. The proportion of patients with reassuring results was 78%, 56%, and 65% for repeat biopsy, MRI, and molecular classifier tests, respectively ( $P < .001$ ) (Fig. 1).

As illustrated in Figure 2, rates of AS were significantly higher for patients with reassuring results, both overall and for each individual confirmatory test (Fig. 2). Specifically, 82% (n = 427) of men with reassuring early confirmatory tests remained on AS, compared to only 52%



\* Reassuring tests include: Prostate biopsy – If original pathology Gleason 6, upgrading to > Gleason 6; if original pathology low-volume Gleason 3+4=7, no longer favorable-risk disease; MRI – PIRADS v2 1-2; Prolaris - <3% probability of prostate cancer mortality, OncotypeDx - >80% freedom from adverse surgical pathology ≤20% high grade disease, Decipher score <0.45.

**Figure 1.** Frequency of reassuring\* early confirmatory test results among men with favorable-risk prostate cancer. \*Reassuring tests include prostate biopsy—if original pathology Gleason 6, upgrading to >Gleason 6; if original pathology low-volume Gleason 3 + 4 = 7, no longer favorable-risk disease; MRI—PIRADS v2 1-2; Prolaris <3% probability of prostate cancer mortality, OncotypeDx >80% freedom from adverse surgical pathology ≤20% high-grade disease, Decipher score <0.45. MRI, magnetic resonance imaging; PIRADS, prostate imaging and reporting data system. (Color version available online.)



\* Favorable-risk prostate cancer: Any volume Gleason 3+3 disease, or low volume Gleason 3+4, defined by 1-3 cores positive with no cores of Gleason 3+4 with > 50% cancer involvement.

**Figure 2.** Proportion of patients with favorable-risk\* prostate cancer remaining on active surveillance according to early confirmatory testing results. \*Favorable-risk prostate cancer: any volume Gleason 3 + 3 disease, or low-volume Gleason 3 + 4, defined by 1-3 cores positive with no cores of Gleason 3 + 4 with >50% cancer involvement. (Color version available online.)

**Table 1.** Proportion of patients with favorable-risk prostate cancer remaining on active surveillance after early reassuring confirmatory test results, by age and grade strata

	≥65	<65	P Value	GS3 + 3 = 6	GS3 + 4 = 7	P Value
Repeat biopsy	85%	93%	.26	92%	60%	.02
MRI	92%	81%	.06	87%	69%	.04
Molecular classifiers	83%	73%	.04	87%	46%	<.01
Overall	86%	79%	.04	88%	51%	<.01

GS, Gleason score; MRI, magnetic resonance imaging.

(n = 157) with nonreassuring results, and 51% (n = 873) of those patients did not undergo early confirmatory testing within 6 months of diagnosis ( $P < .001$ ). Furthermore, although the sample size was small, patients with >1 reassuring confirmatory tests were more likely to adopt AS than those with 1 reassuring confirmatory test (96.2% [n = 25] for 2-3 reassuring confirmatory tests vs 80.6% [n = 408] for 1 reassuring confirmatory test,  $P = .047$ ).

In subgroup analyses, we observed that a larger proportion of patients ≥65 years with a reassuring early confirmatory test remained on AS compared to those <65 years (86% vs 79%,  $P = .04$ ) (Table 1). This finding was consistent for MRI and molecular classifiers, but not for repeat biopsy (MRI: 92% vs 81%,  $P = .06$ ; molecular classifiers: 83% vs 73%,  $P = .04$ ; biopsy: 85% vs 93%  $P = .26$  for ≥65 and <65, respectively). However, only molecular classifiers had statistically significant differences. Similarly, patients with Gleason score 3 + 3 = 6 cancer on their original diagnostic biopsy were more likely to undergo surveillance after a reassuring confirmatory test result than those with Gleason 7 cancer at diagnosis ( $P < .01$ ), with statistical significance for each confirmatory test cohort (Table 1).

In multivariable analyses, receipt of a reassuring early confirmatory test results was significantly associated with persistence on AS (odds ratio 3.6,  $P < .001$ ). Other clinical variables associated with persistence on AS are presented in Table 2.

Our sensitivity analysis evaluating the impact of classifying PIRADS 3 lesions as a reassuring, rather than nonreassuring, MRI result identified no substantive differences from the results of our primary analysis; specifically, 82% (n = 156) of patients with a reassuring MRI persisted on AS compared to 48% (n = 45) with a nonreassuring test result ( $P \leq .01$ ). Next, our sensitivity analyses evaluating the share of reassuring confirmatory tests demonstrated no major differences to our initial findings; namely, 52.2% (n = 90) of patients with low-volume Gleason 3 + 4 disease had reassuring confirmatory tests compared to 43.5% with Gleason 3 + 3 = 6 cancer (Supplementary Table S1), and as described previously, a similar share of patients with Gleason 3 + 3 vs low-volume Gleason 3 + 4 cancer remained on AS with a reassuring confirmatory test (Table 1). Third, our last sensitivity analysis, where we redefined the criteria for a

**Table 2.** Factors associated with persistence of AS 6 months after the diagnosis of favorable-risk prostate cancer

Variable	OR	95% CI	P
Reassuring vs nonreassuring result	3.63	(2.43, 5.41)	<.001
Type of confirmatory test			
Biopsy (reference)			
MRI	0.52	(0.22, 1.22)	.133
Molecular classifier	0.36	(0.17, 0.88)	.024
GS7 vs GS6 (at diagnosis)	0.25	(0.17, 0.39)	<.001
T2a or above vs T1c or less	0.65	(0.36, 1.24)	.201
Race			
African American vs white	0.64	(0.36, 1.04)	.071
Other race vs white	0.98	(0.26, 3.81)	.997
Age	1.04	(1.01, 1.07)	.003
PSA (log)	0.78	(0.57, 1.17)	.264

AS, active surveillance; CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.

“nonreassuring” biopsy as 1 in which patients no longer met criteria for favorable-risk disease, also identified no substantive differences to our findings. In this analysis, 84.1% (n = 74) of patients with biopsy as a confirmatory test and 57% (n = 161) of those with an MRI had a reassuring test; 90.5% (n = 67, P = .009) and 85.7% (n = 138, P ≤ .001) of patients with a reassuring biopsy and MRI remained on AS 6 months after diagnosis.

## DISCUSSION

In Michigan, the use of early confirmatory testing for additional risk stratification is increasing among patients with newly diagnosed favorable-risk PCa who are considering AS. Moreover, rates of AS are significantly higher for patients with reassuring vs nonreassuring confirmatory test results. At the same time, however, a substantial proportion of patients with nonreassuring early confirmatory tests (52%) are persisting with AS. Among patients with reassuring confirmatory tests, higher rates of surveillance were observed for men ≥65 years of age at diagnosis and among those with only Gleason 3 + 3 = 6 cancer on initial biopsy.

Our findings around the rates of reassuring test results are consistent with existing literature describing the frequency of risk reclassification (eg, upgrading) based on repeat biopsy, MRI, and molecular classifiers in other cohorts. A review of repeat prostate biopsy to appropriately risk-stratify patients considering AS demonstrated that 8%-22% of men were upgraded after the second biopsy.<sup>10</sup> However, when the authors compared repeat prostate biopsy to template-guided prostate mapping, they determined that repeat transrectal biopsy failed to detect up to 80% of clinically important cancers. Similarly, in a review of the literature evaluating the ability of MRI to appropriately risk-stratify patients for AS, the authors determined that MRI identified higher grade cancer in 23%-38% of patients who were originally diagnosed with low-risk PCa.<sup>11</sup> Confirming this finding, a meta-analysis of MRI use in pa-

tients undergoing AS for low-risk PCa indicated that MRI identifies an unrecognized significant lesion in 33% of patients; subsequent targeted biopsy of these lesions resulted in 15% of patients no longer meeting criteria for AS based on tumor grade or volume criteria.<sup>12</sup>

For molecular classifier studies, an evaluation of the OncotypeDx test determined that the results of this molecular classifier were considered discordant to the originally diagnosed National Comprehensive Cancer Network risk category in 39% of cases. In addition, the authors found that 18% of providers changed their recommendation for AS in response to the results of the confirmatory test.<sup>13,14</sup> Similarly, an evaluation of the impact of genomic classifiers on treatment decisions determined that the tests changed treatment decisions in 48% of cases; 72% treatment reductions and 27% increases in treatment.<sup>15</sup>

Our study has several limitations. First, our findings from practices in Michigan may not be generalizable to other patients across the United States. However, MUSIC includes both academic and community practices, suggesting that data from patients in our cohort may be more representative than those from single-institution AS cohorts. Second, differences in the accuracy of MRI for identifying PCa lesions, the ability to precisely biopsy the identified lesion at the time of an MRI-transrectal ultrasound fusion biopsy, and the Gleason assignments of different pathologists may vary across institutions in ways that bias our estimates of the proportion of patients with reassuring results. However, these differences reflect real-world practice patterns in diverse academic and community settings. Third, we do not collect data on extraprostatic extension or seminal vesicle invasion identified on MRI; however, if a biopsy was performed, the results of the confirmatory testing are based on biopsy criteria, not on imaging criteria alone. Fourth, the risk of higher grade cancer or disease with a worse prognosis is graded according to results of each confirmatory test (ie, the results are on a continuum and require interpretation, not purely dichotomous), and thus our determination of reassuring and nonreassuring may be different according to patient or physician beliefs and practice patterns. Nonetheless, we included cut-points that have been previously cited in the literature and endorsed on the testing reports provided to patients and physicians.<sup>6-9</sup> Moreover, we performed specific sensitivity analyses to acknowledge differences in opinion around the risk associated with PIRADS 3 lesions on MRI. Fifth, the use of molecular classifier tests has not yet been prospectively validated for risk stratification of patients managed with AS. However, prior evaluations of molecular classifier tests suggest their potential utility in a pretreatment paradigm.<sup>16-20</sup> Sixth, it is unclear whether or not the differences in the proportion of patients with favorable-risk PCa who remain on AS are driven by the physician, patients, or both. However, this manuscript aims to evaluate the current use of early confirmatory testing and whether or not it impacts persistence on AS. With this proof of concept, we can plan additional analyses and data collection relating to physician level variation, how confirmatory testing impacts

counseling, and whether the decision to remain on AS is driven more by the provider or the patient.

These limitations notwithstanding, our findings have important clinical and policy implications. Our initial analyses suggest that results of confirmatory testing are impacting ultimate treatment decisions for men with favorable-risk PCa in a positive fashion, namely, more patients with reassuring results, and therefore more certainty about the lower risk nature of the cancer, are staying on AS and avoiding the potential morbidity of local therapy. That being said, these data are admittedly preliminary and our findings also highlight several additional opportunities and challenges with respect to optimizing treatment decisions in this patient population. First, results of confirmatory testing appear to impact shared decision-making testing differentially based on age and Gleason score criteria; it remains to be seen whether the results of confirmatory tests will be sufficient to change long-standing provider behaviors and patient choice driven by these more conventional measures of cancer risk and life expectancy.

Second, defining the ultimate impact of confirmatory testing for men considering surveillance depends on answers to several additional questions. For instance, if we are going to weigh these tests heavily in our decision for AS, we need to continue to define their prognostic value both in retrospective evaluations of existing cohorts and prospectively following the natural history of patients who choose AS for management of their favorable-risk PCa, conditional on the results of confirmatory tests. In this context, it will also be critical to evaluate each confirmatory test separately.

Likewise, the durability of AS for patients with or without reassuring results needs to be defined with longer term data. This includes the frequency of transitions to local therapy, as well as rates of grade or clinical progression, and analyses of which confirmatory test is associated with the safest and most durable surveillance outcomes. Moreover, confirmatory testing would confer a substantial benefit if it helps identify a group of patients who can safely stay on surveillance over the long-term and potentially even with a lower intensity schedule of follow-up testing. Likewise, it will be important to assess why some patients considering AS are not receiving confirmatory tests, how confirmatory tests impact patient counseling, and whether the tests influence patient satisfaction or regret with treatment decisions. Moreover, our findings specifically highlight the need to better understand the reasons why some patients with reassuring results do not continue with AS, as well as the factors that lead patients to remain on AS even with nonreassuring confirmatory tests. Finally, cost-effectiveness analyses are needed to define the implications of expanded confirmatory testing from a financial perspective.

## CONCLUSION

Collectively, our findings suggest that results of early confirmatory tests may have a significant impact on the initial management strategy of patients with newly diagnosed,

favorable-risk PCa. However, additional research should evaluate the prognostic value of early confirmatory tests, the long-term adoption of AS based on results of confirmatory testing, why some patients are not getting early confirmatory testing, and reasons for continued AS among men with nonreassuring early confirmatory test results. Ultimately, the successful application of early confirmatory testing requires a high degree of utilization coupled with transparent and consistent counseling, and treatment decisions that are concordant with the results and deemed to be clinically valid based on long-term follow-up data.

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## APPENDIX

### SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2018.04.038>.

### EDITORIAL COMMENT



The Michigan Urological Surgery Improvement Collaborative (MUSIC) program has transformed both population management and quality improvement in urology. In the current study,<sup>1</sup> the authors address an important and timely question: do men on active surveillance pursue confirmatory testing after diagnosis of favorable-risk prostate cancer and, when they do, do they persist on active surveillance? In addition to delineating current practices in Michigan of confirmatory testing—the most common being the use of molecular classifiers (55%), followed by magnetic resonance imaging (MRI, 34%) and repeat biopsy (11%), the study also captures a snapshot of how these confirmatory tests are affecting the landscape of active surveillance. Worthy to note

is the meaningful increase in the use of confirmatory testing in men with favorable-risk prostate cancer over the study time, from 25% to 35% of men, evidence of the laudable positive practice changes that MUSIC can affect in a short period.

The initial spirit of noncompetitive collegiality remains a central tenet to MUSIC, which has now grown to now include 90% of urologists in Michigan and 44 sites across the state since its inception in 2011.<sup>2</sup> Similar collaborative approaches to population management include partnerships between specialists and primary care physicians, who can work together to co-manage and work up conditions in an efficient manner specifically targeted to each population.<sup>3</sup> The inclusive, collaborative, rigorous structure and principles of MUSIC remain a shining light and guiding star for all endeavors to improve population health.

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