Appropriateness Criteria for Active Surveillance of Prostate Cancer

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Purpose: The adoption of active surveillance varies widely across urological communities, which suggests a need for more consistency in the counseling of patients. To address this need we used the RAND/UCLA Appropriateness Method to develop appropriateness criteria and counseling statements for active surveillance.

Materials and Methods: Panelists were recruited from MUSIC urology practices. Combinations of parameters thought to influence decision making were used to create and score 160 theoretical clinical scenarios for appropriateness of active surveillance. Recent rates of active surveillance among real patients across the state were assessed using the MUSIC registry.

Results: Low volume Gleason 6 was deemed highly appropriate for active surveillance whereas high volume Gleason 6 and low volume Gleason 3+4 were deemed appropriate to uncertain. No scenario was deemed inappropriate or highly inappropriate. Prostate specific antigen density, race and life expectancy impacted scores for intermediate and high volume Gleason 6 and low volume Gleason 3+4. The greatest degree of score dispersion (disagreement) occurred in scenarios with long life expectancy, high volume Gleason 6 and low volume Gleason 3+4. Recent rates of active surveillance use among real patients ranged from 0% to 100% at the provider level for low or intermediate biopsy volume Gleason 6, demonstrating a clear opportunity for quality improvement.

Conclusions: By virtue of this work urologists have the opportunity to present specific recommendations from the panel to their individual patients.

Abbreviations and Acronyms

AA = African-American

AS = active surveillance

LE = life expectancy

MUSIC = Michigan Urological Surgery Improvement Collaborative

PC = prostate cancer

PSA = prostate specific antigen

PSAD = prostate specific antigen density

RAM = RAND/UCLA Appropriateness Method

SDM = shared decision making

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Community-wide efforts aimed at increasing rates of active surveillance and reducing practice and physician level variation in the choice of active surveillance vs treatment are warranted.

Key Words: watchful waiting, counseling, decision making, prostatic neoplasms, program evaluation

Recent studies indicate increased adoption of AS.[1,2] However, most AS series emanate from academic institutions, large hospitals or prospective trials with defined AS protocols. Very little data exist regarding the adoption of AS across diverse communities in nonprotocol settings.

In the MUSIC, a statewide consortium of academic and community urologists, we reported that 49% of patients with low risk PC were on initial conservative management. However, the rate was highly variable across practices, ranging from 27% to 80%.[2] Data from SEER (Surveillance, Epidemiology, and End Results) cancer registries suggest that initial adoption of AS varies widely in the community.[3,4] In fact, it seems that provider preference accounts for more variation than tumor related factors in the decision of initial treatment vs initial observation.[4]

These studies highlight a need for strategies to disseminate information to the broader urological community about the safety and value of AS. The high variability in the adoption of AS also suggests a need for more consistency in counseling and SDM. One approach is to use guidelines from professional medical societies. However, available guidelines generally provide high level recommendations based mostly on tumor factors and in most cases are not sufficiently granular to apply to the wide variety of individual clinical scenarios seen in everyday clinical practice.

An alternative approach is the RAM,[5] a method originally developed to measure the overuse and underuse of surgical procedures. RAM combines available data with the experience and insight of experts in order to provide guidance at a more detailed level than can be achieved with guidelines. Using RAM, appropriateness criteria with high internal validity have been developed for many procedures.[6]

We used the RAM to 1) review published data and guidelines on AS, 2) develop a list of tumor and patient based parameters that providers consider when counseling, 3) rate the appropriateness of AS for all possible combinations of these parameters and 4) create a counseling guide based on appropriateness scores. We also assessed recent rates of AS in real patients across the state of Michigan with respect to patient and tumor related factors.

METHODS

The proper conduct of the RAM requires several steps, including panelist selection, information synthesis, theoretical scenario development, scenario scoring and analysis. Scores can then be used prospectively or retrospectively to assess practice patterns.

The MUSIC was established in 2011 to improve the quality of prostate cancer care in Michigan. MUSIC now includes 42 community and academic urology practices comprising nearly 90% of urologists in the state. Each participating practice obtained exemption or approval for participation from a local institutional review board.

Previously we found a high degree of variability regarding the use of AS.[2] This was first discussed in a statewide meeting in October 2014. In January 2015 we formed an AS appropriateness criteria panel. A chair (MLC) and co-chair (BRL) were selected, and MUSIC urologists from around the state were asked to nominate themselves for participation in the panel. Final panelists were chosen with a goal of having broad representation from academic and community practices, a stated interest in AS, geographic spread and the availability to participate in several face-to-face meetings.

Practice settings and locations of panelists are described in Appendix 1. A RAM expert (SJB) and 2 patients (1 who underwent radical prostatectomy and 1 on AS) participated in discussions but did not score scenarios. At a preliminary meeting recent data on AS were reviewed with a recognized AS expert (L. Klotz, University of Toronto), and AS guidelines from multiple professional societies including the American Urological Association, National Comprehensive Cancer Network®, American Cancer Society, European Association of Urology, European Society for Medical Oncology, and Agency for Healthcare Research and Quality were presented. For the development of appropriateness criteria the panel agreed on definitions of AS and watchful waiting (Appendix 2). The panel elected to focus on men with low to low-intermediate risk PC and life expectancy greater than 10 years. The most relevant patient and tumor based parameters to be used in the construction of clinical scenarios were discussed.

With input from panelists the chair and co-chair chose tumor and patient based parameters likely to influence counseling (table 1 and Appendix 3). Biopsy tumor burden was based on Gleason score and number/maximal percent involvement of cores. We used PSAD because it appeared to correlate with AS outcomes better than PSA.[7] Patient based parameters included race, LE and sexual importance/function. AA men were given a separate category because of concerns regarding increased oncologic risk.[8,9] Sexual importance/function was included because baseline erectile function and the value or importance a man places on sexual activity can vary highly from one patient to the next. Therefore, the possibility of decreased erectile function associated with treatment may be a highly important consideration for some men but not others. Combining all parameters yielded 160 theoretical clinical

Table 1. *Parameters used for the creation of scenarios*

Biopsy tumor burden	Low vol Gleason 6: 1–2 cores + less than 50% involvement of both cores	Intermediate vol Gleason 6: does not meet criteria for high or low vol Gleason 6	High vol Gleason 6: 6 or more cores, or 3 or more cores each with greater than 50% involvement	Low vol Gleason 3+4: Gleason 3+4 ± 3+3 in 1–3 cores (3+4 cores must have less than 50% involvement)
PSAD (ng/ml/cm^3)	Low (less than 0.15)	High (0.15 or greater)		
Race	AA	NonAA		
LE (yrs)	Medium (10–20)	Long (greater than 20)		

scenarios. Several other parameters were considered but excluded from analysis (Appendix 4).

The scoring of scenarios by panelists was conducted over 2 rounds. Round 1 was conducted privately. Each panelist received a ratings score sheet, definitions and instructions, and the PowerPoint presentations from the preliminary meeting. In accordance with RAM, panelists were instructed to use the available scientific evidence and their best clinical judgment to rate every scenario on a scale of 1 to 9, where 1 indicated that the harms of AS outweighed the benefits, and 9 signified that the benefits of AS outweighed the harms. The scores were associated with RAM terminology ranging from highly inappropriate (score 1) to highly appropriate (score 8 to 9) as well as paradigmatic counseling statements (Appendix 5).

Round 2 scoring was conducted at an in-person meeting (September 2015). Each panelist was provided with an individualized document showing his or her round 1 ratings along with the distribution of round 1 ratings from all other panelists. In other words, for every scenario, every panel member could see where his or her scores stood relative to the scores of the others. Scenarios were discussed and debate was encouraged regarding scenarios with wider dispersion of scores (ie lower agreement). The panel chair moderated the discussion with assistance from the method expert. During the discussion minor changes were made to the counseling statements with the final versions shown in Appendix 5. Panelists understood that the median score and its associated terminology would be the primary end point for each scenario, and disagreement would be assessed by examining standard deviations of scores. Round 2 scoring was completed at the meeting.

In order to understand the degree to which patient based parameters affected the final scores we used an ordinal regression model. The panel scores were grouped as 1, 2 to 3, 4 to 5, 6 to 7 and 8 to 9 to serve as a counseling guide and for the purpose of analysis. An ordinal logistic regression model was fitted to evaluate if PSAD, race, LE and sexual interest/function were associated with round 2 score groups. All analyses were performed using SAS® software version 9.3.

To describe recent real-world practice patterns we queried the MUSIC database for patients with newly diagnosed, low and low-intermediate risk PC registered between January 2012 and May 2015. Patients were stratified by Gleason score, number of positive biopsy cores, PSAD and race, similar to the stratification used by the panel to develop the appropriateness criteria.

RESULTS

AS was favored across 160 clinical scenarios involving men with various biopsy tumor burdens of Gleason 3+3 and small amounts of Gleason 3+4. Median round 2 scores ranged from 8 to 9 (highly appropriate) to 4 to 5 (uncertain) across all scenarios (fig. 1). Importantly no scenario was rated as inappropriate or highly inappropriate. In general, median scores correlated with biopsy tumor burden.

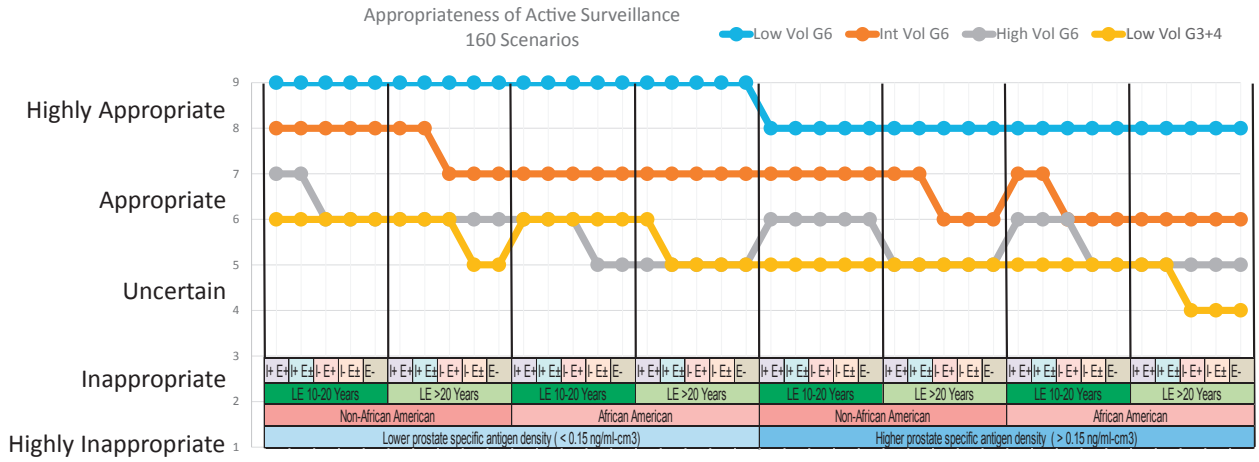

Figure 1. Appropriateness of AS according to 13 MUSIC panelists. Displayed are median round 2 scores for each of 160 clinical scenarios based on biopsy tumor burden, Gleason score, PSAD, race, LE and sexual importance/function. *I*, important. *E*, erections.

Low biopsy volume Gleason 6 was considered highly appropriate for AS no matter what the other parameters were. Intermediate biopsy volume Gleason 6 had slightly lower median scores, ranging from 6 (appropriate) to 8 (highly appropriate). High biopsy volume Gleason 6 and low biopsy volume Gleason 3+4 had similar median scores ranging from 4 (uncertain) to 6 (appropriate). Overall these median scores suggested that the panel of community and academic urologists had a favorable attitude toward AS. The range of scores also suggested that factors other than tumor burden impacted the score for intermediate and high volume Gleason 6 and low volume Gleason 3+4.

For biopsy tumor burdens greater than low volume Gleason 6, ordinal logistic regression showed that PSAD ($p < 0.0001$), LE ($p=0.0004$) and race ($p=0.0015$) significantly impacted the scores, whereas sexual importance/function ($p=0.4635$) had no discernable effect (table 2). Specifically, low PSAD scenarios (less than 0.15 ng/ml/cm^3) had 6.9 times the odds of being in a higher score group (eg 8 to 9 vs 6 to 7 or 4 to 5) compared to high PSAD scenarios. Similarly, nonAA scenarios had 3.9 times the odds of being in a higher score group compared to AA scenarios, and a medium (10 to 20 years) LE had 4.7 times the odds of being in a higher score group score compared to a long LE (greater than 20 years).

Overall there was a high level of agreement among panel members. According to the classic RAM definition for a panel size of 13, disagreement would be noted if 4 scores were 7 or greater and 4 scores were 3 or less. No scenario met this definition of disagreement but we did discern a wide range of standard deviations (fig. 2). These data demonstrate generally lower levels of agreement (higher SDs) among scenarios with higher tumor burdens. The lowest level of agreement occurred in scenarios with a long LE and biopsy tumor burdens of high volume Gleason 6 or low volume Gleason 3+4.

We then examined recent rates of AS in real patients in the MUSIC registry. As illustrated in figure 3, only 55% to 62% of patients with low biopsy volume Gleason 6 were on AS. The rate of AS was lower for other groups. Finally, we assessed variability in rates of AS by urology practice (fig. 4) and individual urologist (fig. 5). As can be seen in these figures, the rate of AS was highly variable, ranging from 0% to 100% at the provider level for patients with low or intermediate biopsy volume Gleason 6. Collectively these data highlight a clear opportunity for improvement in the management of prostate cancer in patients across Michigan.

Table 2. *Odds of clinical scenarios having high scores in favor of AS*

	Odds Ratio Estimates		
Effect	Point Estimate	95% Wald Confidence Limits	
PSAD low vs high	6.932	2.867	16.760
Race nonAA vs AA	3.900	1.679	9.057
LE 10—20 yrs vs greater than 20 yrs	4.695	1.992	10.989

DISCUSSION

The implementation of AS in community settings lags behind that of academic or protocol based settings. Additionally, variability in the use of AS across individual physicians is too high.[2,4,10] How can this be addressed? Guidelines from professional medical societies are generally insufficiently granular to be helpful for individual patients. A central goal of this project was to provide support for counseling sessions beyond what can be found in guidelines. The appropriateness scores allow urologists to present specific recommendations from the panel to individual patients. For example, a patient with 2 cores of Gleason 6 on biopsy could be told that an expert panel of urologists from across the state of Michigan believes that AS is highly appropriate and should be strongly considered. Similarly, a patient with 6 or more cores of only Gleason 6 could be told that the expert panel believes that AS is appropriate or uncertain depending on other parameters such as PSAD and LE. Scores and counseling statements are intended to influence the initial consideration of AS. Additional testing (eg biopsies, imaging, genomic testing) should be used to confirm a decision to continue with AS.

Overall AS was viewed quite favorably by the panel. In particular, no scenario was classified as inappropriate or highly inappropriate. However, higher biopsy volumes of Gleason 6 and low biopsy volume Gleason 3+4 had lower scores. In addition, scoring was affected by race, LE and PSAD, with AA men and those having a longer LE and/or higher PSAD having lower scores. These results reflect the current opinions of panel members.

The scenarios with the least agreement were those with high biopsy volume Gleason 6 or low biopsy volume Gleason 3+4 combined with a long LE (greater than 20 years). Several reasons were articulated for this finding during round 2. Urologists favoring AS would encourage younger, healthier patients to spend more years of their lives without the side effects of treatment. In addition, younger patients are more likely to be sexually active and, therefore, typically accrue greater benefit from the avoidance of treatment side effects. Also, these physicians were more confident that AS protocols would detect tumor progression before metastasis.

On the other hand, others believed that treatment was inevitable and expressed optimism about

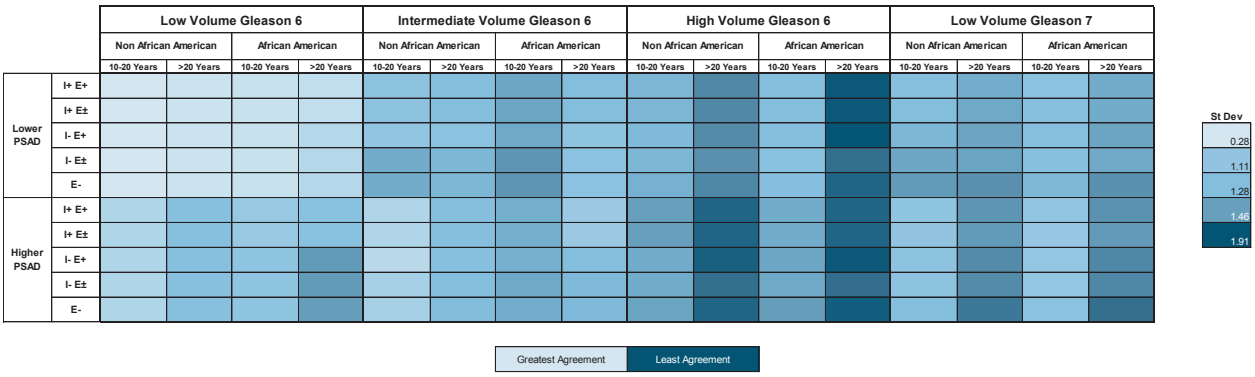

Figure 2. Dispersion SDs of round 2 scores among panelists for 160 clinical scenarios. Darker blue represents lower agreement (higher SD).

the potential for functional recovery after treatment in younger men. Another factor mentioned was the longitudinal burden of AS that involves years of laboratory tests, biopsies and imaging studies. The monitoring burden is obviously greater for men with a greater than 20-year LE and men may become lost to followup. Finally, the possibility of under staging (missing an aggressive tumor) represents a bigger potential loss of life-years for a younger man. Ultimately, the interplay of these factors contributed to lower levels of agreement among the panel members for patients with a long LE and greater tumor burdens.

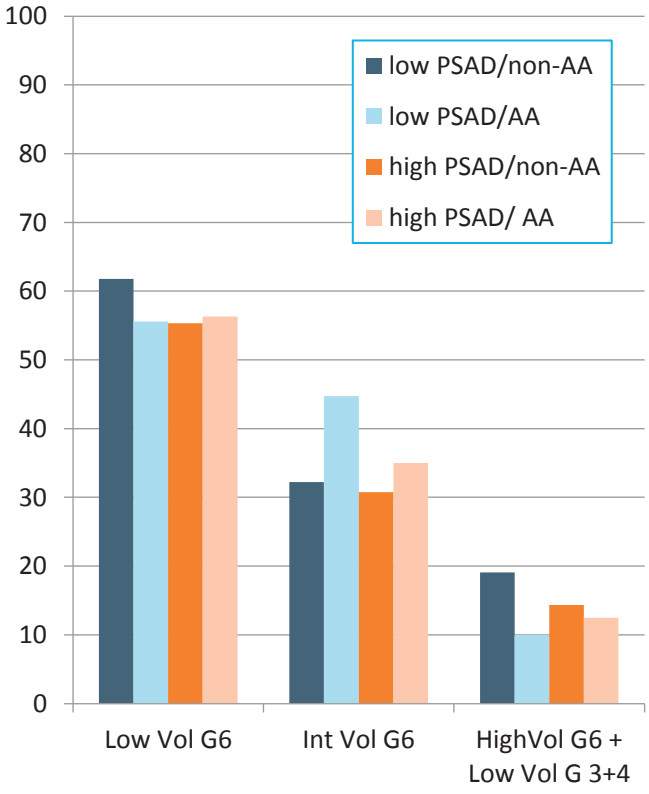

Figure 3. Recent collaborative-wide rates of AS for patient groups based on number of positive biopsy cores, Gleason score, PSAD and race. Low volume Gleason 6 signifies 2 or fewer positive cores, intermediate volume Gleason 6 signifies 3 to 5 positive cores, high volume Gleason 6 signifies 6 or more positive cores and low volume Gleason 3+4 signifies 3 or fewer positive cores.

Preservation of quality of life is one of the stated goals of AS. Thus, it was surprising that sexual function/importance did not have a significant impact on median scores. Therefore, it appeared that urologists may be counseling patients based mostly on other factors. This highlights an opportunity to assess patient preferences explicitly to avoid underestimation of the value that individual patients place on sexual function.

A limitation of our methods was that they did not include patient preferences or clinical variables other than sexual function/importance that might impact the decision. For example, a SDM session may reveal other issues that legitimately steer a man away from AS, including strong family history of PC, severe voiding symptoms, expected low compliance (for a variety of reasons), desire to avoid the long-term burden of AS or significant anxiety. Thus, the panelists expressed strong support for counseling based on appropriateness scores coupled with SDM.

Based on the evaluation of recent AS rates in MUSIC, there is tremendous opportunity to increase rates of AS and reduce variation across our state, despite the fact that we previously reported a high rate of AS.[2] To this end, MUSIC is in the process of rolling out a comprehensive statewide AS pathway that includes life expectancy calculators, an appropriateness scorecard with counseling statements, a decision aid, performance reporting and other tools. Recently Gaylis et al reported on the increased adoption of AS by a large community based urology group practice.[11] This quality

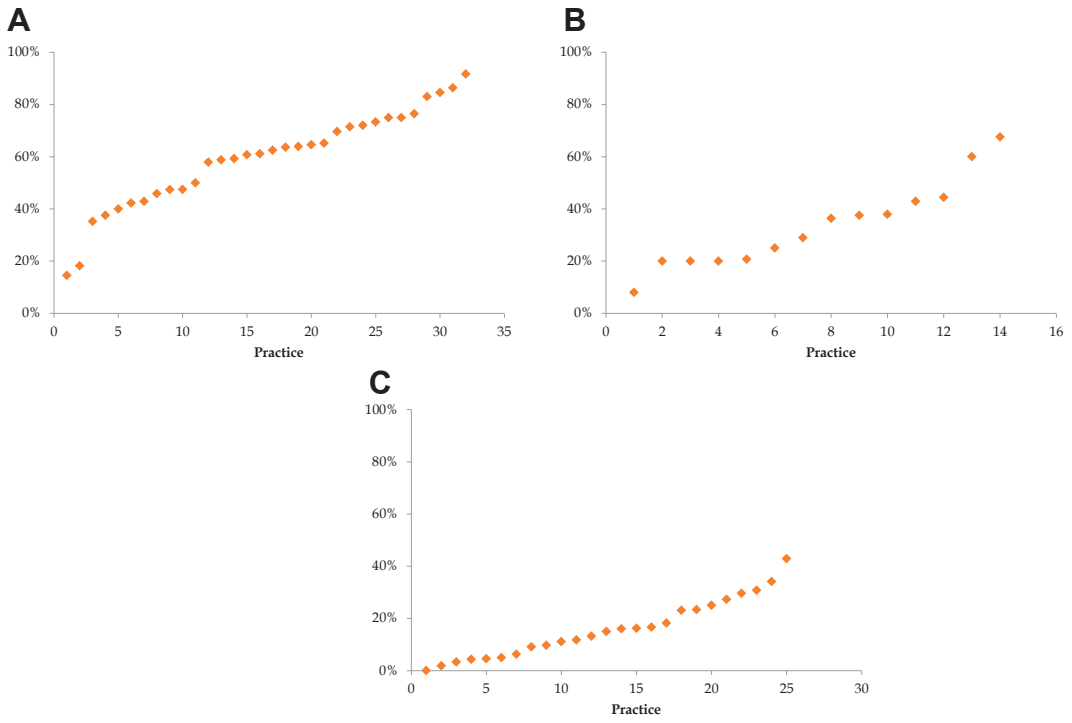

Figure 4. Practice level variation in AS, including low volume Gleason 6 (*A*), intermediate volume Gleason 6 (*B*), and high volume Gleason 6 and low volume Gleason 3+4 (*C*). Data shown for practices with 10 or more patients in each category.

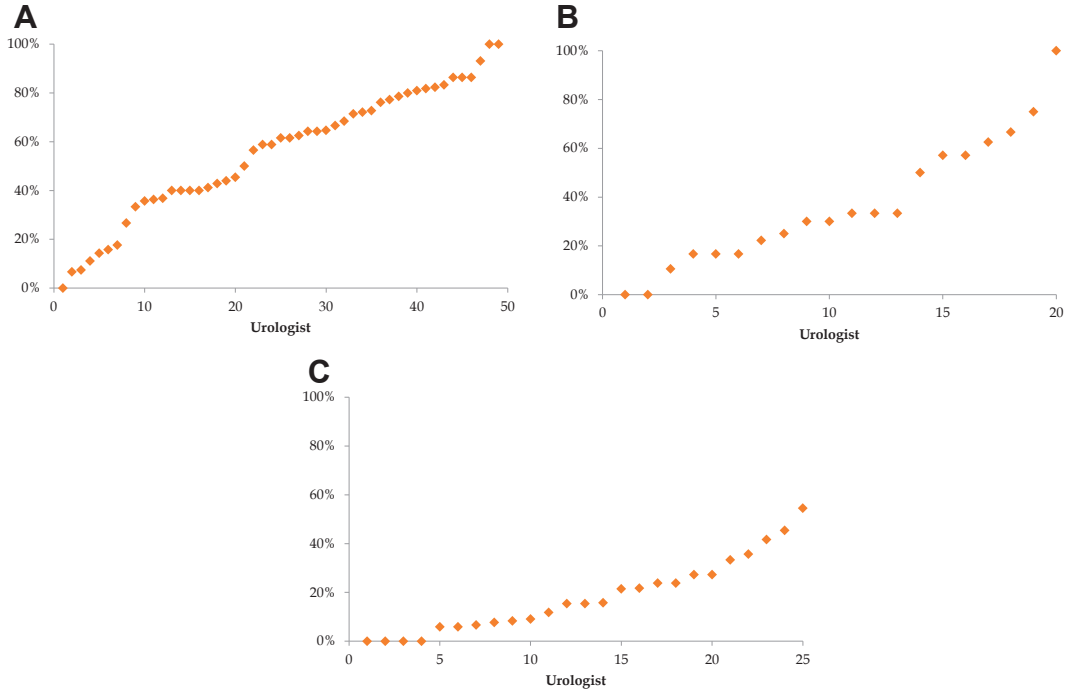

Figure 5. Urologist level variation in active surveillance, including low volume Gleason 6 (*A*), intermediate volume Gleason 6 (*B*), and high volume Gleason 6 and low volume Gleason 3+4 (*C*). Data shown for urologists with 5 or more patients with intermediate volume Gleason 6 and 10 or more patients in other categories.

initiative included a physician educational training program and dashboard comparative-type feedback to individual physicians regarding performance, similar to methods we have used in MUSIC for other quality improvement initiatives. In a similar way we are optimistic that MUSIC's collaborative model will be helpful in rolling out a statewide pathway of AS. In particular, the use of appropriateness scores may lead to more consistency in counseling during SDM sessions. Ultimately we hope to see increased adoption of active surveillance as well as decreased variation among physicians and practices.

In summary, using RAM we created AS appropriateness scores for 160 individual clinical scenarios of newly diagnosed low and low-intermediate risk PC. The scores generally favored AS. These scores and associated counseling statements may be useful in counseling sessions.

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APPENDIX 1

Practice setting and location of panelists

Panelist Background	Urology Practice Setting	Practice Location
Urologist	Academic	Southeastern Michigan
Urologist	Academic Hospital Based	Detroit
Urologist	Academic Hospital Based	Detroit
Urologist	Academic Hospital Based	Western Michigan
Urologist	Academic/Community Hybrid	Suburban Detroit
Urologist	Academic/Community Hybrid	Suburban Detroit
Urologist	Community	Central Michigan
Urologist	Community	Detroit
Urologist	Community	Eastern Michigan
Urologist	Community	Suburban Detroit
Urologist	Community	Suburban Detroit
Urologist	Community	Western Michigan
Urologist	Community	Western Michigan
Internal Medicine / Technical Expert	Not applicable	Not applicable
Patient Advocate	Not applicable	Not applicable
Patient Advocate	Not applicable	Not applicable

APPENDIX 2

Summary of definitions agreed on by the appropriateness panel

Watchful Waiting	Active Surveillance
Complete avoidance of curative intent local therapy	Initial avoidance of curative intent local therapy
Potentially appropriate for low or low-intermediate risk PC	Potentially appropriate for low or low-intermediate risk PC
Appropriate for LE less than 10 years	Potentially appropriate for LE 10 years or more
Disease monitoring by digital rectal examination and/or PSA	Disease monitoring above and beyond digital rectal examination and PSA
Treat only if metastasis	Curative intent local therapy possible in the future

APPENDIX 3

Sexual importance (I) and quality of erection (E) values

I+ E+	Sexual activity important / good erections
I+ E+/-	Sexual activity important / erections not good
I- E+	Sexual activity not important / good erections
I- E+/-	Sexual activity not important / erections not good
E-	Cannot get an erection

APPENDIX 4

Parameters excluded

Parameter	Explanation
LE less than 10 years	Recommendation for watchful waiting
Voiding symptoms	Counseling regarding posttreatment continence problems is similar for all patients
Family history of PC	Degree of family history difficult to define
Biopsy tumor burden greater than low volume Gleason 3+4	Recommendation for treatment

APPENDIX 5

Scoring guide and counseling statements for the appropriateness of AS

Score	RAND/UCLA term	Paradigmatic Counseling Statements
1	Highly Inappropriate	• I am very concerned about delaying your treatment. • You should strongly consider treatment.
2—3	Inappropriate	• I am somewhat concerned about delaying your treatment. • You should consider treatment.
4—5	Uncertain	• I consider both initial delay and initial treatment as reasonable options for you. • The pros and cons are pretty balanced—it is not certain which is better.
6—7	Appropriate	• I have only minor concerns about delaying your treatment. • You should consider AS.
8—9	Highly Appropriate	• I am not concerned about delaying your treatment. • You should strongly consider AS.

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