Review Article

Applying Precision Medicine to the Active Surveillance of Prostate Cancer

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The recent introduction of a variety of molecular tests will potentially reshape the care of patients with prostate cancer. These tests may make more accurate management decisions possible for those patients who have been "overdiagnosed" with biologically indolent disease, which represents an exceptionally small mortality risk. There is a wide range of possible applications of these tests to different clinical scenarios in patient populations managed with active surveillance. ***Cancer* 2015;121:3403-11.** © *2015* The Authors. Cancer published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: prostate cancer, active surveillance, gene expression, biomarker.

INTRODUCTION

The burgeoning area of molecular risk assessment (gene expression profiling and/or proteomic tests) in the diagnosis and treatment of prostate cancer is rapidly illuminating how clinicians might more accurately select the right treatment for the right patient at the right time. Treatment and patient selection and treatment timing form the framework in which clinically available molecular risk profiling tests potentially enhance traditional clinical decision-making. Historically, treatment selection indicated which definitive therapy was chosen (prostatectomy, radiotherapy, etc) and did not include active monitoring of a newly diagnosed patient. Recently, the relative long-term safety of active surveillance (AS) in patients selected based on clinical criteria has been reported.[1] The aforementioned molecular tests have concomitantly been evaluated with respect to the similar, but not entirely equivalent, clinical question: which individual needs treatment?[2-4] The answer lies in the fact that these tests enable management decisions based on the biologic potential of an individual's tumor, thereby allowing a precision medicine approach to the management of patients with early-stage prostate cancer. Accurate assessment of patients' suitability for AS is important at the population level as well. It is expected that 220,800 cases of prostate cancer will be diagnosed in 2015.[5] Recent analyses have demonstrated that the percentage of these cancers that are low risk and/or with a Gleason score $\leq$6 ranges from 22% to 50%,[6,7] and the majority of these patients are likely candidates for AS. However, an estimated 90% of newly diagnosed patients will undergo definitive therapy, highlighting the need to expand AS programs. Herein, we attempted to outline the rationale for the use of molecular risk assessment during counseling of patients regarding AS and posited specific ways in which initial and serial testing might be of value to patients who are managed with AS for increasing lengths of time.

Prostate-Specific Antigen Screening

Before the introduction of prostate-specific antigen (PSA) screening in the early 1990s, observational data suggested that approximately one-half of newly diagnosed prostate cancer cases were locally advanced or metastatic, and that within 5 years of extensive PSA screening this rate decreased to 5%. Due to this precipitous decline in the number of patients initially presenting with incurable disease, along with the belief that all prostate cancer was potentially lethal, continued widespread screening resulted. The practice of screening all men annually starting at age 50 years and continuing indefinitely (which was and in many areas still is a common practice pattern) has resulted in the current issues of overdiagnosis (ie, finding tumors on core needle biopsy performed due to rising PSA that pose no threat to a patient's overall life expectancy) and overtreatment (administration of definitive local therapy without any evidence of a mortality benefit).[8,9] These issues are

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TABLE 1. Molecular Risk Assessment Tests Applicable to Active Surveillance

Assay Name (Company)	Biological Process Measured	Result
Oncotype DX: genomic prostate score (Genomic Health)	RNA quantification/gene expression	Likelihood of freedom from dominant Gleason score 4 and/or non-organ-confined disease
Prolaris: cell cycle progression score (Myriad Genetics)	RNA quantification/gene expression	Estimated 10-y risk of PCSM or 10-y risk of BCR
ProMark: proteomic prognostic test (Metamark Genetics Inc)	Immunohistochemical protein quantification	Likelihood of freedom from dominant Gleason score 4 and/or non-organ-confined disease; Likelihood of Gleason score 6 and ≤T3a disease

Abbreviations: BCR, biochemical disease recurrence; PCSM, prostate cancer-specific mortality.

why, in part, the US Preventive Services Task Force determined PSA screening to be a grade D recommendation, stating that the risks of screening outweigh the benefits.[10] However, this blanket recommendation has not been without controversy, given the nuances of trial design, population characteristics, and subanalyses of what to our knowledge are the 2 most methodologically sound studies of PSA screening to date (the Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer Screening Trial and European Randomized Study of Screening for Prostate Cancer ERPC).[11-13] In addition, worries regarding an increase in avoidable cancer deaths in the absence of screening remain.[14] Nevertheless, the current paradigm is to avoid overtreatment simply by screening no one.

Several recently developed tests such as prostate cancer antigen 3 (PCA3), the 4Kscore (OPKO Health Inc, Miami, Fla), and the Prostate Health Index attempt to more accurately assess, before biopsy, the risk of biologically significant cancer. These tests will aid in avoiding the initial detection of indolent disease, which will help to address the problem of overdiagnosis and, by default, overtreatment. However, for the patients who still undergo biopsy, it is equally important to separately address the problem of overtreatment. The available data suggest that AS is safe for the properly selected patient (ie, one with an indolent tumor and a life expectancy limited by competing causes [age, comorbidity, etc]). The clinical challenge is to increase the accuracy of this selection process. This challenge is met with additional information gleaned from the newly available tests reviewed below (Table 1).

Molecular Risk Assessment as AS Entry Criteria

An individual patient's comfort with AS as a "treatment" course depends directly on the confidence of both the provider and the patient in the accuracy of the assessment of disease indolence based on prostate biopsy. Although there is ample evidence to indicate that Gleason score 6 cancers and select Gleason score 7 cancers are associated with low mortality and morbidity in the absence of therapy (particularly for those individuals with a limited life expectancy), concerns regarding the heterogeneity of clinical behavior within these subgroups and understaging and undersampling issues limit the appeal of surveillance for both patients and physicians.[15,16] It is extremely difficult to know if a needle biopsy that indicates a small focus of low-grade tumor is representative of the entire prostate. For example, increased diagnosis of higher-grade tumors in the often undersampled prostatic apex has been demonstrated.[17] Molecular risk assessment tests have been developed prospectively with tumor heterogeneity in mind,[4] as well as validated retrospectively to account specifically for these biopsy-related issues.[2] Current clinical criteria for AS vary among cohorts, but the majority include parameters such as clinical stage ≤T2a disease, a PSA level ≤10 ng/mL, Gleason score ≤3 + 3 tumors (there are groups that include select patients with Gleason score 3 + 4 tumors), ≤2 to 3 total cores positive, and ≤50% single core involvement.[18] However, approximately 20% of patients with very low-risk disease according to the National Comprehensive Cancer Network (NCCN) guidelines still harbor worrisome pathology. This is one reason why it is not surprising that molecular risk assessment tests have been successful in increasing prognostic precision over and above the performance of known significant clinical covariates and nomograms.

Oncotype DX: genomic prostate score

The genomic prostate score (GPS) (Oncotype DX; Genomic Health, Redwood City, Calif) is comprised of a 17-gene panel derived from representative tumorigenesis pathways prospectively selected based on their combined ability to predict for clinical disease recurrence, death from prostate cancer, and adverse pathology at the time of prostatectomy regardless of whether the tissue analyzed was from the highest Gleason pattern present. The individual gene expression levels are measured as described previously in a minimum sample of 1 mm of tumor and combined algorithmically into the GPS.[19] The GPS is then applied according to the patient's NCCN risk group, giving a predicted percent likelihood of favorable

pathology. In the first clinical validation study, a cohort of men eligible for AS based on clinical criteria, but who underwent early prostatectomy, were analyzed. Consideration of significant clinical covariates in this cohort did not diminish the ability of GPS to predict high-grade and/or non-organ-confined pathology. The odds ratio (OR) for each 20-point increase in GPS adjusted for the continuous University of California at San Francisco Cancer of the Prostate Risk Assessment (CAPRA) score was 2.1 (95% confidence interval [95% CI], 1.4-3.2); when adjusted for NCCN risk group, the OR was 1.9 (95% CI, 1.3-2.8) and when adjusted for age, PSA, clinical stage of disease, and biopsy Gleason score, the OR was 1.9 (95% CI, 1.2-28). This demonstrated that the GPS adds additional clinically meaningful predictive value to prior validated multivariable risk stratification tools.[4] The GPS was also found to be predictive of time to biochemical disease recurrence (BCR) and adverse pathology at the time of prostatectomy after adjusting for NCCN risk group in an additional validation study.[20] Furthermore, a retrospective analysis of the use of GPS in private practice clinics revealed a 24% absolute increase in AS after GPS scores were used in clinical decision-making.[21] Similarly, a prospective clinical usefulness study reported a 10% absolute increase in AS with the use of GPS.[22]

Prolaris: cell cycle progression score

The cell cycle progression (CCP) score (Prolaris; Myriad Genetics, Salt Lake City, Utah) is calculated from an algorithmic analysis of the expression levels of a 46-gene panel in 2 mm to 4 mm of tumor tissue, and is highly correlated with prostate tumor cell proliferation as described previously.[23] In contrast to GPS, the initial development of the CCP score did not account for tumor heterogeneity or biopsy sampling error.[23] However, subsequent retrospective studies have demonstrated conserved predictive value in a biopsy-based setting, despite differences in methodology.[2,24] A meta-analysis of the CCP score demonstrated its predictive value for disease-specific survival (pooled hazard ratio [HR], 2.08) as well as BCR (pooled HR, 1.63).[25] The CCP score also has been shown to improve on clinical predictive models[26] and add value in real-life clinical decision-making. In surveys of ordering physicians, 32% to 65% of cases demonstrated a change in intended treatment after using the CCP score.[27,28]

ProMark: proteomic prognostic test

The ProMark test (Metamark Genetics Inc, Augusta, Ga) is a protein quantification profile that shares principles similar to those of GPS and CCP with regard to development and application. In the initial biopsy simulation study, it was comprised of 12 proteomic biomarkers that were demonstrated to be predictive of aggressive disease and lethal outcome while accounting for biopsy sampling error. This was achieved by creating biopsy simulation tissue microarrays (TMAs) from the areas of highest and lowest Gleason pattern in prostatectomy sample tissue blocks from a cohort of 380 patients. The final predictive model was then tested in both of these TMAs separately. The area under the curve for disease aggressiveness was 0.72 (95% CI, 0.64-0.79) for the low TMA and 0.70 (95% CI, 0.62-0.77) for the high TMA. The areas under the curve were similarly concordant between high and low TMA for lethal outcome.[3] In a subsequent blinded validation study of an 8-biomarker assay derived from the initial markers, the ProMark test improved on clinical risk stratification tools. At a risk score $\leq$0.33, the likelihood of favorable pathology (surgical Gleason score of $\leq 3 + 4$ and organ-confined disease $\leq$T2) for the NCCN very low-risk and low-risk groups was 95% and 81.5%, respectively, compared with 80.3% and 63.8%, respectively, using the clinical criteria alone. A similar improvement on the D'Amico low-risk criteria was observed as well.[29]

Cost concerns

Although the list price of these tests can range in the several thousands of dollars, currently it has been our experience that the out-of-pocket cost to the patient ranges from nothing to a few hundred dollars. As these tests are more widely adopted, increasing coverage by insurance companies can be anticipated, and in the interim there are cost assistance programs available to help mitigate the expense to patients. In addition, we would argue that if the use of these test means getting a clinical decision right the first time, that is ultimately the most cost-effective strategy.

Challenges in the validation of molecular risk profiling tests in AS populations

Even the longest follow-up report in what to our knowledge is one of the largest available AS cohorts[1] does not enable us to determine exactly which patients died of prostate cancer specifically because their choice of surveillance abrogated their chance for cure, as noted by Cooperberg.[30] The studies that are necessary to definitively answer this question may never be performed. However, the available data regarding the added predictive value of molecular risk tests compared with the clinical entry criteria alone used in currently maturing AS series suggests it may be possible to reduce an already low long-term disease-specific mortality risk even further or to maintain this acceptably low

mortality risk while increasing the numbers of patients managed by AS. This "answer by proxy" to the issue raised by Cooperberg[30] relies on the use of molecular risk profiling to more accurately identify, and remove from AS eligibility, men who harbor known risk factors for increased disease-specific mortality that were missed by clinical criteria alone. To this end, the Prolaris and Oncotype DX are now included in the discussion of risk stratification in the latest edition of the NCCN prostate cancer guidelines.[31]

To the best of our knowledge, there are no available, prospective, randomized data that definitively demonstrate which, if any, of these tests outperform current clinical risk stratification in a contemporary AS cohort, nor are there head-to-head comparison data. A multiarm prospective trial of patients choosing AS, randomized to either a molecular profiling test or clinical risk stratification alone to determine final AS eligibility, could more definitively answer some of these unknowns. However, these studies would require lengthy follow-up to examine clinically meaningful endpoints, during which time it is likely that interim technological advances would supplant the test versions used during trial enrollment.

Molecular Risk Profiling as a Substitute for Early Confirmatory Repeat Biopsy

Early repeat biopsy as entry criteria into an AS protocol has been widely advocated due to the aforementioned issues of undersampling and understaging.[18,32,33] However, a firm consensus regarding timing and type (standard transrectal ultrasonography [TRUS] biopsy vs saturation vs magnetic resonance-ultrasound fusion biopsy) of the repeat evaluation of patients managed by AS does not exist. Some may say that repeat evaluation is unnecessary given the findings in low-risk or older patients in the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) trial and the overall findings of the Prostate Cancer Intervention versus Observation Trial (PIVOT), in which watchful waiting (ie, doing nothing until symptom development) did not appear to confer an increased mortality risk.[34,35] Even as this question is debated, the underlying issue remains that repeat biopsy is subject again to the same drawbacks as initial biopsy, including patient discomfort, sampling error, and risk of infection. No patient who has undergone a prostate biopsy desires to repeat the experience unnecessarily, and the need for multiple biopsies may be the determining factor for some patients to elect treatment over continued AS.[36,37] Furthermore, avoiding a repeat biopsy will avoid the small, but real, risk of urinary sepsis and/or mortality that Ehdaie et al found to be increased after each subsequent biopsy in an AS cohort.[38] Approximately 1 million prostate biopsies are performed every year in the United States among Medicare patients.[39] If even 10% of these biopsies are for AS, with a conservatively estimated 1% sepsis risk, avoiding them altogether would save 1000 patients from hospitalization annually.

If obtained at the time of the initial biopsy, molecular risk profiling can potentially substitute for the need for early repeat biopsy based on its prior referenced ability to predict the biology of the entire prostate, thereby assuaging concerns regarding undersampling and understaging. Although not initially developed in a predefined AS population, both the GPS and CCP score have been validated in biopsy specimens of patients who meet the clinical criteria for AS.[2,4] The initial discovery study for ProMark (Metamark Genetics Inc) was also performed in a cohort of patients who were potentially eligible for AS.[3]

In addition, Long et al demonstrated that there is a strong correlation of gene expression across separate biopsy cores from the same patient,[40] a finding that was similar to that of a study by Peng et al that suggested that there was limited, operator choice-dependent variation in gene signature analysis of highly expressed genes across multiple biopsy samples, primary versus secondary Gleason patterns, and primary versus benign tissue.[41] This consistency of gene expression, regardless of interbiopsy or intrabiopsy tumor heterogeneity, reinforces the current understanding that it is possible to be confident in the biology of the entire prostate based on analysis of gene expression in a biopsy sample.

Some may argue that these tests report only a probability of adverse pathology versus repeat biopsy, which directly confirms the absence of unfavorable features (and in turn equates to a low likelihood of important upgrading). However, uncertainty exists with both approaches, and it is currently unclear whether one approach differs substantially in risk from the other. Another concern may be the clinically apparent low-risk patient with a discordantly high-risk test score. In these cases, repeat biopsy may be unavoidable. Although the implementation of concomitant molecular risk profiling with initial TRUS biopsy as a replacement for early repeat biopsy is a nuanced proposition that currently lacks direct comparison data, we believe it to be a reasonable approach given the aforementioned arguments that these tests accurately predict the biologic potential of the entire tumor regardless of sampling error or intratumor heterogeneity.

Can Molecular Risk Assessment Make for More Intelligent AS Follow-Up?

There is currently a range of reported follow-up biopsy intervals for patients managed by AS, with no available

data, to our knowledge, supporting the use of one frequency over another and no reports regarding the safety of modifying follow-up intervals based on clinical risk factors.

Although prospective data regarding the stability of individual patients' molecular risk scores over time have yet to be reported, important inferences can be made from the clinical validation studies that may help to encourage individual tailoring of AS follow-up schedules. In addition to the ability of GPS to predict the initial presence of adverse pathology, both GPS and the CCP score are backed by 15-year follow-up data demonstrating their predictive ability with regard to risk of clinical disease recurrence (GPS) and metastasis-free survival (CCP score).[2,4] Therefore, one can hypothesize that when applied as prospective selection criteria for an AS cohort, the patients with the lowest likelihood of adverse pathology would also be likely to have the most stable molecular risk scores over time, intuitively demonstrating the possibility of a decreased frequency of monitoring without sacrificing mortality benefit.

In patients who undergo molecular risk stratification at the time of initial diagnosis that demonstrates a low likelihood of adverse pathology, a longer interval to repeat biopsy, or perhaps even conversion to a watchful waiting protocol, could be considered.[42] Conversely, among patients with a higher likelihood of adverse pathology, a shorter interval to repeat biopsy or a more confident decision for immediate treatment may be made. Although this rationale is based on robust retrospective follow-up data, definitive support for this strategy would come in the form of randomization of patients to more intensive or less intensive follow-up based on their molecular risk profile. Molecular risk profiling adds prognostic precision to known clinical parameters; it does not replace them. Clinicians must still exercise judgment regarding the factors of patient life expectancy, comorbidity, and patient desire when using a molecular risk score to help plan the frequency of follow-up in an individualized AS protocol (Fig. 1).

Molecular Risk Assessment Versus Histopathology

Concordance among pathologists with regard to Gleason grading and reporting practices of the extent of cancer varies widely, adding to the difficulty in ensuring uniform and accurate prognostication.[43,44] McKenney et al examined an AS cohort and demonstrated that there was low interobserver reproducibility with regard to deciding between tangentially sectioned Gleason pattern 3 versus poorly formed glands of Gleason pattern 4 on needle biopsy, which, they acknowledge, has been reported in other cohorts as well.[45,46] This pathologic gray zone between Gleason score 6 and score 7 tumors could account in part for the wide distribution of molecular risk scores in individual clinical risk categories based on Gleason grade (ie, a patient with an NCCN low-risk cancer has a 77% average probability of favorable pathology at the time of prostatectomy, but with the addition of GPS, that same patient has a probability of favorable pathology ranging from 55% to 86%). An additional contributing factor to the likelihood that Gleason score 6 cancers are becoming more biologically homogenous and Gleason score 7 cancers are increasingly heterogeneous is the ongoing Gleason grade migration that has been reported in both the United States and Europe[47,48] as a result of changes in how Gleason scores are assigned.[49] Furthermore, it has been suggested that a small percentage of patients managed by AS may receive different treatment recommendations at follow-up biopsy based on the definition of histopathological progression used.[50]

Validated molecular risk assessment tests provide an easily exportable, consistent level of objectivity, independent of local pathologic expertise, potentially rendering an even greater increase in prognostic precision than previously reported in cohorts undergoing centralized pathologic review. Their use can also potentially mitigate some of the interpatient variability that is introduced by varying pathologic interpretation. This added knowledge is particularly helpful in more confidently recommending AS to some patients with Gleason score 7 cancers with molecular risk scores that indicate a low likelihood of adverse pathology as well as providing additional peace of mind to a patient with very low-risk Gleason score 6 cancer who is choosing AS.

Multiparametric Magnetic Resonance Imaging as an Adjunct to Molecular Profiling

Multiparametric magnetic resonance imaging (MP-MRI) provides localization information to help guide the biopsy of suspicious areas, has a negative predictive value for Gleason score >6 of 80% to 90%, and increases the likelihood of finding a Gleason score 7 tumor on biopsy.[51-53] Despite these valuable clinical characteristics, MP-MRI still cannot distinguish which of these tumors needs to be treated to decrease disease-specific mortality risk. In contrast to the molecular risk tests previously reviewed, to our knowledge there are no long-term follow-up data regarding MRI in the AS population. MP-MRI also does not detect all tumors.[54] In addition, there is substantial "art of medicine" in MRI interpretation with an associated learning curve during implementation of this technology.[55]

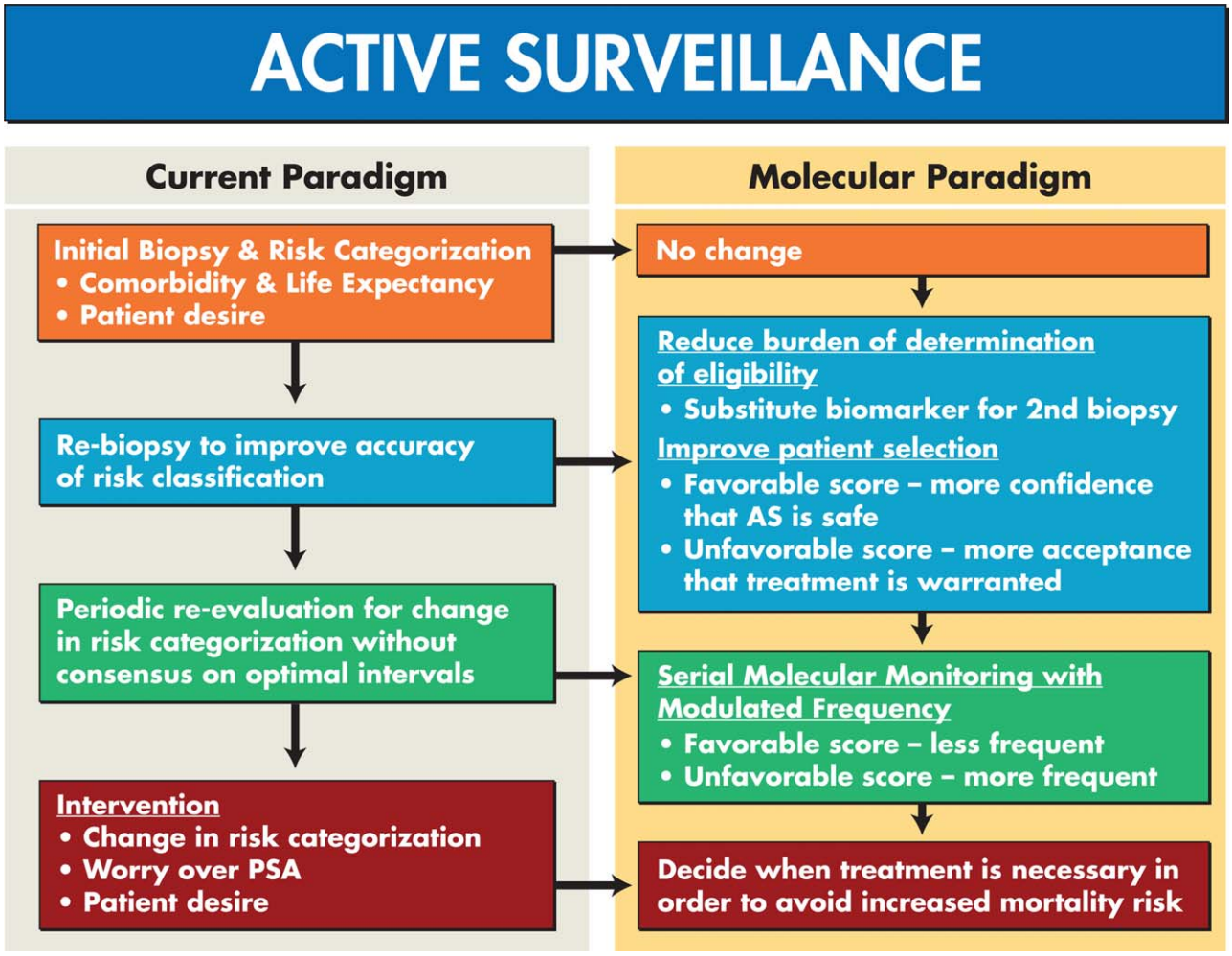

Figure 1. Incorporation of molecular risk profiling into active surveillance (AS) protocols. PSA indicates prostate-specific antigen.

MP-MRI represents an important information-gathering tool during the initial evaluation for AS eligibility. However, to the best of our knowledge there is insufficient evidence to suggest that it can be used as a proxy for early repeat biopsy or to safely modify follow-up biopsy frequency in patients managed by AS. Rather, MP-MRI is likely to find its place as an adjunct to molecular risk profiling in further refining initial prognostic decision-making in patients managed by AS.[56]

Does the Patient's Race Matter?

Recently, the safety of AS in African American (AA) patients has been called into question.[57] The experience at Johns Hopkins demonstrates that AA men undergoing prostatectomy are more likely to have adverse pathology and BCR than their white counterparts of the same NCCN risk group.[58,59] In AA men eligible for AS, higher rates of pathologically non-organ-confined disease as well as anteriorly located dominant nodules that may escape sampling by standard TRUS biopsy also have been reported.[60,61] Jalloh et al examined 237 AA men in a cohort of 4231 patients classified with NCCN low-risk disease and found a significantly higher positive surgical margin rate in AA men, but no difference in rates of upstaging or upgrading at the time of prostatectomy.[62] Offering AS to AA men has been debated in the literature with both the "pro" and "con" view suggesting that AS still can be offered to AA men if it is done in a careful manner while counseling patients regarding "elevated oncologic risks."[63,64]

Molecular risk assessment is one possible way to help level this potentially uneven playing field for AA patients who meet the clinical criteria for AS. The initial validation studies of GPS did not explicitly account for racial variation and the percentage of AA patients was moderately low (12% and 10%, respectively, of patients in the biopsy study and prostatectomy study; only 3% in

the validation study).[4] However, in a subsequent validation study of an independent cohort of 402 patients at 2 US military centers, 20% were AA (82 patients) and there were no significant racial differences noted with regard to the GPS distributions.[20] GPS prediction of BCR and adverse pathology at the time of prostatectomy was found to be similar between white and AA patients (HR for time from biopsy to BCR per 20 GPS units, 2.97 vs 3.50, respectively; and OR for adverse pathology per 20 GPS units, 4.05 vs 2.86, respectively). The CCP score development studies and subsequent validation in AS-eligible cohorts do not report race distribution. However, the CCP score was found to be predictive of BCR and prostate cancer-specific mortality in a cohort of patients undergoing primary external-beam radiotherapy, approximately one-half of whom were AA.[65] To the best of our knowledge, the racial distribution of patients used to develop the ProMark test is also currently unknown.[3]

There is some encouraging evidence that molecular risk profiling may be powerful enough to overcome racial biases that are present with other forms of clinical risk stratification. Further application of these tests to validation cohorts with larger percentages of AA men, as well as other races, will hopefully increase confidence that these tests can be used with the same reliability regardless of an individual patient's race.

Conclusions

In the setting of current clinical staging and risk prognostication methods, AS has rendered very positive results, with a variety of studies demonstrating cancer-specific survival rates that are at or near 100%. However, these studies represent a fraction of the number of men who are eligible for AS. To safely increase the number of patients who are managed with AS, the negative predictive value of whichever combination of clinical nomogram and molecular risk profiling is used must be high enough so that the cancer-specific survival rates of patients who are managed with AS do not fall below those of patients who are immediately treated. This is especially pertinent given the decreasing average age of the patient being managed by AS.[66] We believe that molecular risk profiling can help to improve risk stratification for patients being evaluated for and subsequently followed on AS, while reducing some of the associated clinical and psychological burden.

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