ASCO special articles

Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline

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abstract

PURPOSE This guideline provides recommendations for available tissue-based prostate cancer biomarkers geared toward patient selection for active surveillance, identification of clinically significant disease, choice of postprostatectomy adjuvant versus salvage radiotherapy, and to address emerging questions such as the relative value of tissue biomarkers compared with magnetic resonance imaging.

METHODS An ASCO multidisciplinary Expert Panel, with representatives from the European Association of Urology, American Urological Association, and the College of American Pathologists, conducted a systematic literature review of localized prostate cancer biomarker studies between January 2013 and January 2019. Numerous tissue-based molecular biomarkers were evaluated for their prognostic capabilities and potential for improving management decisions. Here, the Panel makes recommendations regarding the clinical use and indications of these biomarkers.

RESULTS Of 555 studies identified, 77 were selected for inclusion plus 32 additional references selected by the Expert Panel. Few biomarkers had rigorous testing involving multiple cohorts and only 5 of these tests are commercially available currently: Onco*type* Dx Prostate, Prolaris, Decipher, Decipher PORTOS, and ProMark. With various degrees of value and validation, multiple biomarkers have been shown to refine risk stratification and can be considered for select men to improve management decisions. There is a paucity of prospective studies assessing short- and long-term outcomes of patients when these markers are integrated into clinical decision making.

RECOMMENDATIONS Tissue-based molecular biomarkers (evaluating the sample with the highest volume of the highest Gleason pattern) may improve risk stratification when added to standard clinical parameters, but the Expert Panel endorses their use only in situations in which the assay results, when considered as a whole with routine clinical factors, are likely to affect a clinical decision. These assays are not recommended for routine use as they have not been prospectively tested or shown to improve long-term outcomes—for example, quality of life, need for treatment, or survival. Additional information is available at www.asco.org/genitourinary-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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With panel representation from the American Urological Association (AUA), the College of American Pathologists (CAP), and European Association of Urology (EAU). At the time of publication, this ASCO Guideline has been endorsed by the EAU.

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INTRODUCTION

This clinical practice guideline evaluated evidence to provide physicians, including medical oncologists, radiation oncologists, and urologists; other health care practitioners (eg, nurses, nurse practitioners, and physician assistants); patients; and caregivers with recommendations regarding the role of molecular diagnostics in localized prostate cancer.

Prostate cancer is the most commonly diagnosed cancer in men in the United States (approximately 174,650 in 2019), nearly 20% of all new cancers, and the second leading cause of cancer-related death (approximately 31,620 in 2019).[1] At diagnosis, there is a diverse spectrum of clinical courses that range from indolent features with a negligible likelihood of morbidity or mortality to characteristics reflecting near certitude of eventual metastases and cancer-specific death. Predicting future clinical behavior is imperfect but constitutes the foundation of physician counseling and patient management decisions. Potential ramifications of various management strategies on quality of life and cancer-specific outcomes are highly variable and often profound. Risk stratification has traditionally relied on serum prostate-specific antigen (PSA),

THE BOTTOM LINE

Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline

Guideline Question

Are there molecular biomarkers with utility in the management of localized prostate cancer?

Target Population

Men with localized prostate cancer.

Target Audience

Medical oncologists, radiation oncologists, urologists, other health care practitioners, patients, and caregivers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Summary. Numerous molecular biomarkers have been developed to improve risk stratification and patient management. Few panels have undergone extensive validation; however, five are commercially available and have been shown in retrospective analyses to provide additional information beyond standard clinical models in prognostication or patient selection for therapy. While these tissue-based tests may improve risk stratification when added to standard clinical parameters, we recommend considering their use in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Examples include select men with high-volume low-risk or favorable intermediate-risk prostate cancer considering active surveillance, or in men with high-risk features for treatment intensification (Table 1: Summary Boxes Recommendations 1-4). While testing may influence management decisions, there is no high-level evidence to indicate that the results from these panels improve quality of life or cancer-specific outcomes. There have been additional biomarkers evaluated that do not have sufficient data to be clinically actionable or are not commercially available. We recommend continued investigation of tissue-based molecular biomarkers in the context of clinical trials.

Clinical Question 1

Are there molecular biomarkers to identify patients with prostate cancer who are most likely to benefit from active surveillance?

Recommendation 1.1. Commercially available molecular biomarkers (ie, Onco*type* Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 1.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Clinical Question 2

Are there molecular biomarkers to diagnose clinically significant prostate cancer?

Recommendation 2.1. Commercially available molecular biomarkers (ie, Onco*type* Dx Prostate, Prolaris, *Decipher*, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate).

Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Clinical Question 3

Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation?

Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic

(continued on following page)

THE BOTTOM LINE (CONTINUED)

biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Clinical Question 4

What are the comparative strengths and weakness of genomics versus magnetic resonance imaging in identifying clinically significant prostate cancer?

Recommendation 4. In men with newly diagnosed prostate cancer eligible for active surveillance, both magnetic resonance imaging and genomics intend to identify clinically significant cancers. The Expert Panel endorses their use only in situations in which the result, when considered with routine clinical factors, is likely to affect management. This may include, for instance, the initial management of men who are potentially eligible for active surveillance, where each of these approaches may provide clinically relevant and actionable information. These tests may provide information independent of routine clinical parameters and independent of one another (Type: Informal consensus; benefits/harms ratio unknown; Evidence quality: Low; Strength of recommendation: Weak).

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines. Patient information is available at www.cancer.net

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Gleason grading, and clinical stage to classify localized cancers as low, intermediate, or high risk. Using additional biopsy data (eg, total number or percentage of positive cores), more nuanced risk stratification can be achieved (eg, University of California Cancer of the Prostate Risk Assessment score and/or nomograms).[2,3]

A variety of molecular biomarkers have been developed, evaluated, and commercialized with an overarching aim to further personalize risk stratification, more comprehensively inform management decisions, and consequently improve the quality of care. Biomarkers may be assessed from blood, body fluid, or tumor tissue with the intention of adding clinically actionable data independent of previously attained information (ie, PSA, Grade Group, and/or clinical stage). The goal of a biomarker is to achieve any, or ideally all, of the following: estimate the likelihood of a disease characteristic being present or absent, more accurately determine prognosis, or provide the probability of response to a specific treatment.

To evaluate the localized prostate cancer biomarker studies to date, ASCO formed an Expert Panel. The potential role of molecular biomarkers in 4 clinical scenarios was addressed: determining patients who are most likely to benefit from surveillance of localized prostate cancer, identifying prostate cancers with the potential to ultimately cause symptoms or develop metastases, deciding between adjuvant or salvage radiation therapy (RT) after radical prostatectomy, and assessing the relative value of genomics versus magnetic resonance imaging (MRI). The purpose of this clinical practice guideline is to provide recommendations that are based on the best available evidence regarding the role of molecular, cellular, and genomic biomarkers in localized prostate cancer. As these biomarkers are relatively new and the field is rapidly evolving, future directions are also discussed. Table 2 provides operational definitions for the terms used within this guideline.

GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions: Are there molecular prostate cancer biomarkers with which to identify patients who are most likely to benefit from active surveillance? Are there molecular biomarkers to diagnose clinically significant prostate cancer? Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation? What are comparative strengths and weakness of genomics versus MRI in identifying clinically significant prostate cancer?

Additional nonclinical research questions of interest to the Expert Panel were: What are optimal approaches for tumor selection and processing for molecular testing? How to interpret assay characteristics (eg, reproducibility, quality of tissue, and tumor heterogeneity)? How should biomarkers with purely prognostic implications be used? What is the utility and generalizability of prognostic assays developed in

TABLE 1. Summary Boxes Recommendations 1-4

Clinical question 1: Are there molecular prostate cancer biomarkers with which to identify patients who are most likely to benefit from active surveillance?
Summary: There are currently commercially available biopsy-based multigene expression classifiers (ie, Decipher, Onco*type* Dx Prostate, and Prolaris) and one protein-based biomarker (ProMark). Each seems to independently improve the prognostic accuracy of clinical multivariable models for identifying men with biologically significant disease. The clinical benefit of integrating these classifiers in selecting patients for surveillance has not been prospectively demonstrated. There are no comparative data indicating that one may be more accurate than another.
Example clinical scenario: These may be considered, for instance, in select men with NCCN low- or favorable intermediate-risk prostate cancer who might benefit from refined risk classification when considering active surveillance (eg, high-volume Grade Group 1; Grade Group 1 with abnormal DRE or high PSA density; low-volume Grade Group 2).
Recommendation 1.1. Commercially available molecular biomarkers (ie, Onco*type* Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
Recommendation 1.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).
Clinical question 2: Are there molecular biomarkers with which to diagnose clinically significant prostate cancer?
Summary: There are commercially available biopsy-based multigene expression classifiers (ie, Decipher, Onco*type* Dx Prostate, and Prolaris) and a protein-based biomarker (ProMark). While these assays may also inform patients considering active surveillance (Recommendation 1), additional prognostic value may contribute to risk stratification and patient counseling when added to standard clinical parameters. The ability of these tests to improve outcomes (quality of life and risk of metastasis or death) has not been prospectively evaluated. Comparative studies between tests have not been reported.
Example clinical scenario: These may be considered, for instance, in select unfavorable intermediate-risk patients when deciding whether to add androgen-deprivation therapy to radiation therapy.
Recommendation 2.1. Commercially available molecular biomarkers (ie, Onco*type* Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).
Clinical question 3: Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation?
Summary: If a radical prostatectomy exhibits adverse pathologic features (≥ T3a, node positive) and the PSA is undetectable, the Decipher Genomic Classifier may help risk stratify men and identify those who are most likely to benefit from postoperative adjuvant versus early salvage radiotherapy. These retrospective studies currently lack prospective validation and long-term follow up.
Example clinical scenario: A man with adverse pathology at prostatectomy (eg, Grade Group 3-5, T3a, margin positive) an undetectable PSA, and early postoperative continence. Decipher Genomic Classifier may inform the decision of adjuvant radiation *v* observation. If radiation, it may also inform whether to include concomitant androgen deprivation.
Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).
Clinical question 4: What are the comparative strengths and weakness of genomics *v* MRI in identifying clinically significant prostate cancer?
Summary: Both MRI and genomics may help identify clinically significant prostate cancer. There have been few studies directly comparing genomics with MRI. Two used multiparametric MRI with the 17-gene Genomic Prostate Score (Onco*type* Dx) and one compared multiparametric MRI with a genomic classifier (Decipher). The data suggest that MRI and genomics can each provide clinically relevant information regarding the likelihood of upgrading on subsequent biopsy or at prostatectomy. Furthermore, there are patients for whom MRI and genomics can provide independent and actionable information.
Example clinical scenario: If there are concerns of unsampled high-grade cancers within the prostate, MRI would be favored to guide targeted biopsy. To optimize the understanding of the natural history of a biopsy-detected intermediate-risk cancer (eg, Grade Group 2-3), genomics would be favored.
Recommendation 4. In men with newly diagnosed prostate cancer who are eligible for active surveillance, both MRI and genomics intend to identify clinically significant cancers. The Expert Panel endorses their use only in situations in which the result, when considered with routine clinical factors, is likely to affect management. This may include, for instance, the initial management of men who are potentially eligible for active surveillance, where each of these approaches may provide clinically relevant and actionable information. These tests may provide information independent of routine clinical parameters and independent of one another (Type: Informal consensus, benefits/harms ratio unknown; Evidence quality: Low; Strength of recommendation: Weak).

Abbreviations: DRE, digital rectal examination; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen.

TABLE 2. Definitions and Terms Used in the Guideline

Molecular biomarker	A biologic molecule found in blood, body fluid, or tissue that provides information regarding the presence or absence of a disease, prognosis, or likelihood to respond to a specific treatment. Molecular biomarkers broadly encompass DNA, transcriptome, protein, metabolic, and other tissue-based or cellular biomarkers.
Cellular biomarker	Cells found in blood, body fluid, or tissue that provides information regarding the presence or absence of a disease, prognosis, or likelihood to respond to a specific treatment.
Genomic biomarker	Genetic material, including DNA or RNA, found in blood, body fluid, or tissue that provides information regarding the presence or absence of a disease, prognosis, or likelihood to respond to a specific treatment.
Active surveillance	Monitoring prostate cancer rather than immediately treating it.
Clinically significant prostate cancer	Various definitions; in general, clinical, pathologic, or biomarker features of prostate cancer suggesting a possibility of becoming clinically relevant (symptoms or metastases).
Low-risk prostate cancer	Gleason Score $\leq$ 6 (Grade Group 1), PSA $<$ 10 ng/mL, and nonpalpable or only palpable in less than half of one lobe of the prostate (clinical stage T1c or T2a).
Intermediate-risk prostate cancer	PSA 10-20 ng/mL, a clinical stage of T2b-T2c, or a Gleason Score 7 (Grade Group 2-3) grade without meeting any criteria for high risk
High-risk prostate cancer	Clinical stage T3a, Gleason Score $\geq$ 8 (Grade Group $\geq$ 4), or PSA $\geq$ 20 ng/mL.
Very high-risk prostate cancer	Clinical stage T3b-T4, any primary Gleason pattern 5 (Grade Group 5), or $>$ 4 cores of Gleason Score 8-10 (Grade Group $\geq$ 4).
Assay validity	Comprehensive experiments that evaluate and document the quantitative performance of an assay, including sensitivity, specificity, accuracy, precision, reproducibility, detection limit, range, and limits of quantitation.
Analytic validity	How well a test predicts the presence or absence of a particular disease, condition, or state.
Clinical validity	How well the test result is related to the presence, absence, or risk of a specific disease.
Clinical utility	The ability of a screening or diagnostic test to prevent or ameliorate adverse health outcomes, such as mortality, morbidity, or disability.
Tumor heterogeneity	Variability among cancer cells, including cellular morphology, genomic alterations, gene expression, metabolism, proliferation, and metastatic potential.
Predictive biomarker	Provides information regarding response to a specific treatment.
Diagnostic biomarker	Provides information regarding the likelihood of disease presence or absence.
Prognostic biomarker	Provides information about the patients' overall cancer outcome (eg, disease recurrence, progression, death) independent of treatment received.

a non–Clinical Laboratory Improvement Amendments (CLIA) setting?

The following questions were also identified for future topics: How should germline carriers with DNA repair alterations (eg, *BRCA, ATM*, or *CHEK2*) be screened for prostate cancer or managed following the diagnosis? Are there molecular biomarkers by which to select men for prostate biopsy? Are there molecular biomarkers to predict which patients with clinically localized disease are most likely to benefit from surgery versus radiation? Are there molecular biomarkers to decide if hormonal therapy should be added to RT and for how long?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and ASCO guidelines staff with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via multiple teleconferences and corresponded through e-mail. Based on consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Guideline recommendations were available for 2 weeks, allowing the public to review and comment after submitting a confidentiality agreement. These were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review, and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. The final version was reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of this project was provided by ASCO.

Recommendations were developed using a systematic review of clinical trials, other comparative studies, and

clinical experience. The PubMed database was searched on September 12, 2018, for evidence published within the previous 5 years (January 2013 through to the end of August 2018) and updated in February 2019 (to the end of January 2019) using the following criteria:

- Population: men with localized prostate cancer
- Research question 1 concepts: biomarkers (molecular, cellular, genomic), active surveillance, prostate cancer
- Research question 2 concepts: biomarkers (molecular, cellular, genomic), clinically significant, prostate cancer
- Research question 3 concepts: biomarkers (molecular, cellular, genomic), prostate cancer, postprostatectomy, adjuvant versus salvage radiation
- Research question 4 concepts: biomarkers (molecular, cellular, genomic) versus MRI, detection of prostate cancer

There were 7,076 references obtained in the initial PubMed search. After committee review of the titles and abstracts, 555 were retained. Of those 555, 131 went on to full-text review, 77 were retained, and an additional 32 papers were identified by panelists, bringing the total to 109 papers. The actual searches used and included terms can be found in Data Supplement 1.

Articles were excluded if they were meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; and published in a non-English language. The guideline recommendations were crafted, in part, using the Guidelines into Decision Support methodology.[4] In addition, a guideline implementability review was conducted and revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Expert Panel and guidelines staff worked with cochairs to keep abreast of the need for guideline updates. Based on formal review of the emerging literature, ASCO determines the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict.

RESULTS

A total of 108 studies were obtained to provide the evidence base. Twenty studies[5-24] were obtained to answer research question 1: Are there molecular prostate cancer biomarkers to identify patients who are most likely to benefit from active surveillance? (Data Supplement 4). Eighty-five studies[5,6,11,14-16,18-20,22-96] were obtained to answer research question 2: Are there molecular biomarkers to diagnose clinically significant prostate cancer? (Data Supplement 5). Twelve of these studies[5,6,11,14-16,18-20,22-24] were also included in the evidence base for research question 1. Fourteen studies[97-110] were obtained to answer research question 3: Are there molecular biomarkers to guide the decision of

postprostatectomy adjuvant versus salvage radiation? (Data Supplement 6). Three studies[111-113] were obtained to answer research question 4: What are the comparative strengths and weaknesses of genomics versus MRI in identifying clinically significant prostate cancer? (Data Supplement 7).

RECOMMENDATIONS

CLINICAL QUESTION 1

Are there molecular biomarkers with which to identify patients with prostate cancer who are most likely to benefit from active surveillance?

Recommendation 1.1

Commercially available molecular biomarkers (ie, Onco*type* Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 1.2

Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Qualifying statements. After large-scale sequencing studies reported distinct genomic subclasses of prostate cancer, several single-gene somatic aberrations were assessed for their relationship with outcomes. The most common, *TMPRSS2-ERG* gene fusion, which is present in approximately 50% of prostate cancers, has not been consistently associated with clinical outcomes,[114] whereas loss of the tumor suppressor *PTEN* (20% of localized prostate cancers) was found to be prognostic in several small studies.[115] Germline DNA mutations (eg, *BRCA1, BRCA2, MSH*) are present in a subset of men with prostate cancer (approximately 4% to 6% of patients with localized prostate cancer and 12% metastatic),[116] and *BRCA2* has been associated with adverse outcomes, such as higher rates of progression on active surveillance and inferior metastasis-free and overall survival after primary treatment.[19,117,118] Recommendations for germline testing in localized prostate cancer is beyond the scope of this guideline and a matter of continued discussion.[119] In addition to DNA aberrations, several transcriptome (mRNA) and protein-based biomarkers have been developed. There are commercially available biopsy-based multigene expression classifiers (ie, Decipher, Onco*type* Dx Prostate, and Prolaris) and one that is protein based (ProMark), as well as several other single-gene or protein assays that have been tested (but not as well validated) to risk stratify men who are considering active surveillance. Validated assays should only be used when the assay result, when considered as a whole with routine clinical factors, is likely to affect management. For instance, these may be considered in select men with National Comprehensive Cancer Network (NCCN) low- (high-volume Gleason 6 – Grade Group 1) or favorable intermediate-risk prostate cancer (typically Gleason Score 3 + 4 = 7, percentage of positive biopsy cores < 50%, and no more than one NCCN intermediate-risk factor) who are considering active surveillance and might benefit from refined risk classification.

Literature review, analysis, and clinical interpretation. Twenty studies[5-24] were obtained (Data Supplement 4). Management decisions in localized prostate cancer are generally centered around the use of prognostic clinical and pathologic factors to assess tumor aggressiveness and natural history. However, the prognostic accuracy of an isolated clinicopathologic variable—Grade Group, clinical stage, and PSA—is limited. Multivariable models, such as NCCN risk categories, University of California Cancer of the Prostate Risk Assessment score, or the Memorial Sloan Kettering Cancer Center nomogram, substantially improve prognostic accuracy over individual variables.[2,3] Thus, the central question regarding molecular biomarkers in the setting of newly diagnosed patients who are potentially eligible for active surveillance is whether risk stratification is substantially improved compared with widely available clinical models.

Although several studies have identified and assessed various biomarkers in prostate cancer, few assays have been well validated in active surveillance cohorts. Of these, three biopsy-based multigene expression classifiers and one protein-based assay have undergone evaluation using retrospective cohorts and are commercially available to assist with initial risk stratification (Onco*type* Dx Prostate, Prolaris, ProMark, and Decipher; Table 3). Each seems to independently improve the prognostic accuracy of clinical multivariable models for identifying men with biologically significant disease.[12,15,18,23,24,33] While developed around variable end points (eg adverse pathology at prostatectomy and risk of metastasis), published data are consistent with each of these providing additional prognostic information beyond standard clinical models, although the extent of supporting data and studies significantly varied among assays. There are currently no comparative data that indicate whether one may be more accurate than another and limited data to support the specific risk thresholds provided on the individual testing reports.[120] In addition, a clinical genomic risk grouping scheme has been developed for one of these genomic classifiers, but has not yet been validated or prospectively evaluated in a newly diagnosed favorable-risk cohort.[33]

Although molecular classifiers may improve initial management decisions for some patients, the long-term impact of including or excluding patients for surveillance based on

TABLE 3. Description of Assays

Test(s)	Company	List Price,* USD	Sample Requirement	Clinical Utility/Intended Use	Comments
Decipher Biopsy and Decipher Postoperative	Decipher Biosciences (formally Genome Dx)	$5,150	FFPE tissue from prostate biopsy, or	Categorize patients into low/high risk to stratify patients to surveillance *v* treatment (and intensity of treatment)	Evaluates mRNA expression levels of 22 genes from FFPE tissue; generates score from 0 to 1.0
			Prostate tissue after RP	Postprostatectomy for patients with adverse pathologic features to guide whether surveillance, adjuvant, or salvage therapy may be warranted	
Oncotype Dx GPS	Genomic Health	$4,520	Tumor tissue from original biopsy in neutral buffered formalin; prostatectomy specimens not accepted	Biopsy-based likelihood of adverse pathologic features (Grade Group ≥ 3 or extracapsular extension); identify those who may benefit from surveillance *v* treatment	GPS ranges from 0 to 100 based on mRNA expression of 17 genes across four pathways
Prolaris Biopsy and Prolaris Postprostatectomy	Myriad Genetic Laboratories	$3,900	FFPE tissue from: prostate tumor biopsy, or prostatectomy specimens	Aggressiveness of cancer; provides a 10-year risk of metastasis after definitive therapy, and disease-specific mortality under conservative management	mRNA expression of cell-cycle progression genes are used to calculate the score; clinical factors are subsequently added for risk assessment
ProMark, Proteomic Prognostic test for prostate cancer	MetaMark	$3,900	Requires tissue collected with patented biopsy kit available from MetaMark	Uses automated image recognition technology to determine the likelihood of Grade Group ≥ 2 or stage ≥ T3b	Expression of 8 proteins; uses automated image recognition technology to generate a score from 1 to 100 indicating the aggressiveness of prostate cancer

Abbreviations: FFPE, formalin fixed, paraffin embedded; GPS, Genomic Prostate Score; RP, radical prostatectomy.

*Cost was not available on the Web site and was therefore obtained by contacting sales team or customer support for each company during the week of April 22, 2019. List prices do not necessarily reflect prices paid by Medicare or out of pocket by patients or other discounted rates.

these assays has not been properly evaluated. Recent data suggest that the use of these tests will affect decisions for some patients, but longer-term data will be needed to validate whether this leads to improvements in quality of life or cancer-specific outcomes.[11,14,27,121,122] In particular, given the data from the ProtecT trial demonstrating relatively low rates of metastases or prostate cancer–specific mortality associated with active monitoring, additional prognostic information may only be necessary for a subset of patients being considered for surveillance.[123] This group, if one exists, most likely includes men with higher volume Grade Group 1, men with favorable intermediate risk (eg, Grade Group 2, percentage of positive biopsy cores < 50%, and no more than one NCCN intermediate-risk factor), discordant features in their risk stratification (eg, palpable mass with Grade Group 1), or other features associated with progression while on active surveillance (eg, high PSA density and certain germline or somatic mutations). Currently, there are no strong data or expert guidelines to support active surveillance in otherwise healthy men with Grade Group 3 or higher cancer; therefore, we would consider the use of genomic biomarkers only in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect a physician's recommendation or a patient's choice for surveillance versus treatment, but they should not be used routinely.

Emerging evidence suggests that specific germline mutations—*BRCA2*, in particular—may predispose men to more aggressive prostate cancers[6,19] as well as higher grade reclassification while on active surveillance.[6] It is unclear whether these men would benefit from early treatment, more frequent surveillance, or standard surveillance. While there is still insufficient evidence in the favorable-risk setting to make strong recommendations regarding the impact of these mutations on active surveillance eligibility, risk and benefits should be discussed and, at minimum, close monitoring for those patients with germline mutations who opt for surveillance is prudent.

CLINICAL QUESTION 2

Are there molecular biomarkers with which to diagnose clinically significant prostate cancer?

Recommendation 2.1

Commercially available molecular biomarkers (ie, Onco*type* Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 2.2

Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Qualifying statements. Accurate risk stratification and staging are of paramount importance for men with newly diagnosed localized prostate cancer as they consider various management approaches; however, prognostic uncertainty regarding disease progression remains, with a significant proportion of men and their physicians selecting treatment when surveillance may have sufficed. As described previously, several tissue-based molecular biomarkers have been identified and assessed to putatively optimize the diagnosis of clinically significant prostate cancer; mRNA-based panels (ie, Decipher, Onco*type* Dx Prostate, Prolaris) and a protein assay (ie, ProMark) are commercially available (Table 3). There have been many additional biomarkers evaluated that do not have sufficient data to be clinically actionable or are not commercially available. Although the available assays may also inform patients regarding the suitability of active surveillance—discussed in Recommendation 1—additional prognostic value may also help guide risk stratification, patient counseling, and management decisions when proceeding with treatment. An example may be in men with unfavorable intermediate-risk prostate cancer when deciding whether to add androgen-deprivation therapy to radiation.[96] The Expert Panel endorses their use in situations in which the assay results, when considered in combination with routine clinical factors, is likely to affect management. Routine use of these tests for diagnosing clinically significant prostate cancer should not be offered.

Literature review, analysis, and clinical interpretation. Eighty-five studies[5,6,11,14-16,18-20,22-96] were obtained to answer research question 2 (Data Supplement 5), which were mostly small case series with limited follow up or validation. Four commercially available tests (Decipher, Onco*type* Dx Prostate, Prolaris, and ProMark; Table 3) have been shown to independently improve the prediction of clinically significant end points, with variable levels of supporting data, and to potentially improve clinical decision making. Although they may more optimally characterize men with low- and favorable intermediate-risk disease, the guideline panel cautions against their routine use. The ability of these tests to improve outcomes (eg, quality of life, risk of metastasis or death) has not yet been prospectively tested. Use of a validated tissue-based molecular biomarker is reasonable in select men for whom the management decision would be affected by the results, in conjunction with standard tumor and patient-specific factors. Examples may include a man with low-risk prostate cancer but high-volume Grade Group 1, favorable intermediate risk, or other situations in which the addition of genomic data may strongly influence the decision to proceed with surveillance or treatment. Another example may be patients with intermediate-risk disease when deciding whether to add androgen-deprivation therapy to radiation. Comparative studies between tests and across several patient risk categories are still needed. In addition, future comparisons with improved clinical prognostic models[124] and enhanced prebiopsy imaging are mandatory.

An essential consideration when implementing any tissue-based biomarker study in prostate cancer is that tissue-based molecular testing is dependent on the site of collection within the primary tumor and tumor content, and is significantly influenced by the heterogeneity of the disease.[68,125,126] For the purpose of improving prognostic value, it is of paramount importance to select the areas that are characterized by the most aggressive disease. The dominant index lesion may not always be obvious in a multifocal prostate cancer or may be undersampled.[127] Identification and selection of these areas to biopsy may be aided by novel and improved imaging at diagnosis and/or testing prioritized after systematic review of multifocal lesions postprostatectomy. Finally, when a germline association or familial cancer is suspected,[119,128] genetic counseling and clinical testing based on germline DNA sequencing using a cancer predisposition gene panel is recommended. Data are still emerging regarding the optimal screening and management of carriers of germline DNA mutation.

While many studies have suggested that other tissue-based tests (eg Ki67, PTEN loss, somatic copy number variation, EZH2 overexpression, and several others) may offer insight into diagnosing significant disease, there is currently insufficient evidence to support their clinical use. Moreover, results from these are often dependent on technical aspects that may introduce significant variability when comparing methodologies or results between performing sites. Understanding reproducibility, concordance between methods, and other performance metrics are needed for emerging and future biomarkers.

CLINICAL QUESTION 3

Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation?

Recommendation 3.1

The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 3.2

Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Qualifying statements. When PSA is undetectable after radical prostatectomy, the value of adjuvant radiation is an area of debate and clinical controversy. Several molecular biomarkers have been developed to inform this decision (Data Supplement 6), with only the Decipher Genomic Classifier and PORTOS biomarker commercially available. The Expert Panel recommends consideration of Decipher Genomic Classifier in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. This may be in situations in which a high Decipher score, for instance, helps to inform patient counseling in making a decision to precede with adjuvant radiation and/or the duration of androgen deprivation in combination with radiation. However, in the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered.

Literature review, analysis, and clinical interpretation. Following radical prostatectomy, PSA is a quick, widely available, and inexpensive biomarker with attractive specificity and sensitivity. When undetectable, the decision to pursue adjuvant or early salvage radiation, if needed, is complex and guided by several factors, including age, comorbidity, life expectancy, urinary/erectile function, patient preferences around toxicity and risk, and aggressiveness of the tumor. While clinical and pathologic factors may inform this shared decision-making process, there remains a lack of clarity in determining whether an individual will have clinical benefit from further treatment. While one randomized phase III trial (SWOG 8794) has demonstrated improved metastasis-free and overall survival with adjuvant radiation in men with pT3 disease with a number needed to treat to save one life of approximately nine,[129] two other trials did not demonstrate a survival advantage.[130,131] In addition, more than 60% of such men remain metastasis free at 10 years without postoperative radiation, suggesting that many men may avoid RT and associated potential for adverse effects. The current unmet need is to identify men who are most likely to have clinical benefit from further therapy. Thus, biomarkers may help to better risk stratify those most likely to benefit from postoperative adjuvant versus early salvage RT. Early salvage RT appears to have a greater benefit than delayed therapy and molecular biomarkers to identify men at lower risk who may benefit from RT alone or men at high risk who may require more intensive therapy, such as androgen-deprivation therapy, androgen receptor inhibition, and/or taxane chemotherapy.

We identified 14 relevant studies[97-110] of biomarkers in the postprostatectomy setting (Data Supplement 6), none of which is based on randomized prospective controlled studies. Several genomic biomarkers are independently associated with adverse outcomes, including the number of copy number alterations and the Decipher Genomic Classifier biomarker (Table 3). The Decipher Genomic Classifier biomarker has been independently validated, supporting its prognostic value independent of grade, stage, margin status, and PSA. The Decipher low-risk subset of men had excellent long-term clinical outcomes irrespective of the timing of postoperative RT (ie, adjuvant vs early salvage). In men with Decipher intermediate- to high-risk tumors, outcomes were poor but improved in men who received early postoperative RT, particularly in the adjuvant setting, compared with those who did not. The Decipher PORTOS signature is the only predictive biomarker for RT response with a benefit observed in the subset of men with high PORTOS scores who received RT. These retrospective studies currently lack prospective validation and long-term follow-up in a controlled trial and therefore do not provide strong evidence to support their routine use. They provide prognostic information about PSA relapse rates and the risks of metastasis or death over time. Such information may be important in counseling patients regarding the overall risks and benefits of postoperative radiation and potentially informs escalation of the duration of androgen deprivation in combination with radiation. These signatures are being evaluated using tissue and clinical outcomes from several prospective NRG Oncology clinical trials (ClinicalTrials.gov identifiers: NCT00767286, NCT00005044, NCT00002597, and NCT00002874).

CLINICAL QUESTION 4

What are the comparative strengths and weaknesses of genomics versus MRI in identifying clinically significant prostate cancer?

Recommendation 4

In men with newly diagnosed prostate cancer who are eligible for active surveillance, both MRI and genomics intend to identify clinically significant cancers. The Expert Panel endorses their use only in situations in which the result, when considered with routine clinical factors, is likely

to affect management. This may include, for instance, in the initial management of men who are potentially eligible for active surveillance, where each of these approaches may provide clinically relevant and actionable information. These tests may provide information independent of routine clinical parameters and independent of one another (Type: Informal consensus, benefits/harms ratio unknown; Evidence quality: Low; Strength of recommendation: Weak).

Literature review, analysis, and clinical interpretation. There is increasing use of both MRI and genomics to identify clinically significant prostate cancer, with much of the data focused on their prognostic value. In general, MRI-guided biopsies have increased the detection of higher-grade cancers[132]; however, approximately 10% to 15% of clinically significant cancers are invisible by MRI.[133] Several genomic tests have demonstrated the capacity to predict the likelihood of adverse pathologic findings at prostatectomy, risk of recurrence, metastases, or death[67,134]; however, there have been few studies directly comparing genomics and MRI. Three studies[111-113] were obtained to answer research question 4 (Data Supplement 7). Two used multiparametric MRI with the Genomic Prostate Score (GPS) Onco*type* Dx expression profile, and one compared multiparametric MRI with the Decipher Genomic Classifier.

GPS values were compared with MRI lesions using a modified Prostate Imaging Reporting and Data System (PI-RADS) version 1 system, classifying MRI findings as negative, indeterminate, or positive.[112] An increase in mean rank GPS with increasing MRI PI-RADS score across the whole population was noted. Yet, GPS scores within a specific PI-RADS score widely varied and among men with Grade Group 1, and GPS did not correlate with PI-RADS score.[111]

There was also a wide and overlapping distribution of GPS across PI-RADS2 version 2 scores among a cohort of men with low- to intermediate-risk prostate cancer on biopsy.[30] No significant difference in Decipher scores from PI-RADS 1 to 3 versus 4 versus 5 lesions was noted, suggesting these scores are independent of PI-RADS. On multivariable analysis, the only factors associated with Grade Group 2 at prostatectomy were high-risk Decipher score and increasing age. High-risk genomic classification can be seen across all combinations of PI-RADS categories and Grade Group 1 and 2, suggesting a potential use for genomic testing in men with low- to favorable intermediate-risk prostate cancer.

The primary clinical context in which genomic biomarkers and multiparametric MRI overlap is in the initial management of men who are potentially eligible for active surveillance. The data show that each of these approaches can provide clinically relevant information regarding the likelihood of upgrading on subsequent biopsy or at prostatectomy. Furthermore, there are patients for whom MRI and genomics can provide independent information, suggesting a potential role for using both MRI and genomics in certain situations. However, this increase in testing intensity would clearly increase cost, and it is not clear which specific patients may benefit from both.

There are no long-term prospective data for either MRI or genomics in men with newly diagnosed prostate cancer. Yet with the ability to assess genomic profiles from archival specimens, retrospective tissue analyses of genomic classifiers from prospective studies are providing insights. In comparison, while the data supporting MRI to identify high-grade prostate cancers are robust, there are no long-term MRI data with meaningful end points. In addition while MRI has been widely incorporated into active surveillance pathways, the only prospective RCT in this setting did not find a difference in upgrading rates between the MRI and non-MRI arms.[135]

Clinical deployment of MRI and genomics in newly diagnosed men should take into account the strengths and limitations of each of these tests and the clinical question being asked. Genomic information can be limited by multifocality if the most biologically aggressive lesion is missed on biopsy, whereas MRI may miss some of these lesions because of invisibility. For example, in men with very low-risk disease, the primary question may be whether there is a missed index lesion, and MRI may provide the most information. In contrast, for men with favorable intermediate-risk disease, the primary question may be the underlying biologic aggressiveness of this cancer, and genomic classifiers may provide the most value. Whether the benefits outweigh the costs of using both approaches in some men—for example, MRI followed by targeted biopsy, then genomic assessment—requires additional study.

DISCUSSION

While standard assessment tools for risk stratification are informative, prostate cancers may behave uncharacteristically with natural history or relapse patterns that are sometimes unpredictable. Similar clinical and histologic patterns at diagnosis may lead to variable clinical outcomes across patients. Consequently, biomarkers that are capable of significantly improving risk stratification, distinguishing indolent versus aggressive prostate cancer, remains an unmet need. Ideally, a biomarker would enhance the quality of patient counseling and provide increased assurance for a particular management strategy.

Molecular, cellular, and genomic information have the potential to improve upon clinical criteria by providing unique insights into the underlying tumor biology, such as cellular proliferation, differentiation, and androgen receptor signaling, as well as identifying unique vulnerabilities that may affect local or systemic treatment response. These characteristics, when added to clinicopathologic features, would ideally provide valuable diagnostic, prognostic, or predictive information to improve patient counseling and

shared decision making, and ultimately improve meaningful outcomes, such as quality of patient care, quality of life, or quantity of life.

Several tissue-based prostate cancer biomarkers have been developed, commercialized, are widely available, and covered by insurance carriers. Decipher (GenomeDx Biosciences, Vancouver, BC, Canada), Onco*type* Dx (Genomic Health, Redwood City, CA), and Prolaris (Myriad Genetics, Salt Lake City, UT) are mRNA-based gene expression classifiers, and ProMark (Metamark Genetics, Waltham, MA) is a proteomic test amenable to formalin-fixed paraffin-embedded prostate biopsy or prostatectomy tissues. Several retrospective analyses have supported their potential to identify appropriate patients for active surveillance (Question 1) or predict adverse pathologic, biochemical, or cancer-specific survival outcomes (Question 2). These data could potentially improve confidence in management choice, especially in gray zone areas in which clinical variables are less certain, although high-quality prospective evidence, particularly in a randomized design, is currently lacking. The Decipher genomic expression score can also be helpful in selecting appropriate patients for adjuvant versus salvage radiation (Question 3). Identifying patients with poor prognosis may ultimately lead to therapy intensification, including the escalation of local therapy or addition of newer systemic agents, a focus of several ongoing trials.

Despite the promise of molecular biomarkers in addressing these important unmet clinical needs, there is currently insufficient evidence to recommend the routine use of these tests. The costs of testing and downstream therapy implications are considerable and currently not justified for routine use, financially or oncologically, based on available evidence. While these tissue-based tests may improve risk stratification, we recommend their use only in situations in which a specific assay result, when considered in combination with routine clinical factors, will clearly affect the management decision. These assays have not been prospectively tested nor shown to improve intermediate or long-term outcomes (eg, QOL, need for treatment, or survival). Rigorous and prospective clinical testing is warranted and strongly encouraged.

Although the routine use of molecular biomarkers is not recommended, the Expert Panel recognized that there may be scenarios in which biomarkers may be helpful to inform prognostication or to guide management decisions. For instance, men who are considering active surveillance of newly diagnosed prostate cancer with higher-risk features for progression (eg, high-volume Grade Group 1, low-volume Grade Group 2, or high PSA density) may benefit from a biomarker, although the committee recognizes that a relative minority of men will attain clear actionable data as test results are often equivocal in this scenario. For men struggling to determine whether adjuvant versus early salvage postprostatectomy RT is most appropriate, biomarker data may provide additional data to integrate into the final decision.

Which of the available commercial biomarkers is best (if any) in these settings cannot be determined as these assays have not been sufficiently compared head to head in properly designed studies. However, the extent of supporting data significantly varied among the assays. Furthermore, understanding their use in the context of MRI imaging is also of great importance (Question 4). There are insufficient data to support a consensus statement on the relative value of genomics versus MRI; however, for an individual patient, MRI or genomic testing may ultimately provide overlapping, complementary, or discordant information. Comprehensive studies with comparative data, costs, and clinical implications would be valuable.

Additional challenges exist for molecular biomarker development in prostate cancer. Tumor heterogeneity may occur within an individual, meaning two or more independent prostate cancer foci may exist within a patient, each harboring different characteristics. Identifying the most informative (eg, index or driver lesion) for biomarker testing may be a challenge, particularly given the known undersampling that occurs with prostate biopsy. Furthermore, molecular changes, as with any biologic process, are not always definitive or binary, as there is a biologic spectrum even within risk groups. Understanding if and how available assays complement other prognostic factors, such as germline DNA mutations (eg *BRCA1/2*, *MSH*, and others), may also influence future testing and management decisions. Studies including diverse racial and ethnic groups are essential to inform broader applicability of testing. Finally, cost-effectiveness analyses that incorporate the price of testing along with cost savings and quality of life gained from sparing ineffective treatment will be critical.

Despite several challenges ahead and the lack of current evidence to support a committee consensus for routine genomic biomarker testing, there is continued optimism regarding the potential for tissue-based biomarkers to inform decision making for certain men and, we hope, improve outcomes for men with prostate cancer.

SPECIAL COMMENTARY

In additional to the primary research questions, the following questions were also considered as the Expert Panel believed they warrant discussion despite the absence of evidence.

What Is the Optimal Approach for Tumor Selection and Processing for Molecular Testing?

In contrast to prostatectomy specimens, prostate biopsies offer unique challenges to molecular testing because of their small size, particularly in active surveillance populations, and their often limited volume of cancer. Furthermore, at the histopathologic level, prostatic adenocarcinoma is often intermingled with benign prostatic glands with variable

amounts of intervening stroma, both of which may affect the robustness of molecular tissue testing. Therefore, pathologists are instructed to select areas of highest tumor density. For RNA-based tests, a single 1-mm core punched from the tumor is generally sufficient to obtain a test outcome, but more tissue is needed for DNA-based tests. Although cutoff values may depend on the platform used, a tumor density of at least 40% may be acceptable for commercially available RNA-based tests.[136]

Prostatic adenocarcinomas are morphologically heterogeneous, and evidence is emerging that particular architectural tumor patterns associated with Gleason pattern 4, such as stromogenic, cribriform, and intraductal carcinoma may have stronger (adverse) prognostic implications than other grade 4 patterns.[137,138] One study demonstrated that the selection of such areas for molecular testing yielded more adverse prognostic scores using the Decipher test, suggesting that more detailed histopathologic analysis might substitute for some of the information gained by a molecular test.[139] In contrast, grade within a carcinoma focus did not significantly affect RNA test scores.[126] These observations would suggest that pathologists should primarily select areas of highest cellularity and specific adverse pathology growth patterns for molecular testing. Furthermore, individuals with multifocal prostate cancer may harbor both low-grade and high-grade foci with distinct prognostic gene expression signatures,[127] suggesting that molecular assessment of a low-grade tumor identified on prostate biopsy may not always provide meaningful information in the setting of coexisting but undersampled (or unsampled) high-grade foci.

Interpreting Assay Characteristics (eg, reproducibility, quality of tissue, and/or tumor heterogeneity)

US Food and Drug Administration–approved assays, such as Decipher, Prolaris, and Onco*type* Dx, have met rigorous quality criteria, including reproducibility, linearity, analytical accuracy, and precision.[140] They also contain a panel of reference household genes by which to assess their analytical accuracy for a given sample[22,23,141] at predescribed RNA input levels, accounting for variations in tissue quality. Inter- and intratumoral heterogeneity offer the greatest challenges to accurate molecular tissue testing of prostate cancer: Approximately 80% of prostatectomy specimens are multifocal, with generally one dominant or index lesion of highest pathologic grade and/or largest size,[142] and in approximately 60% of patients with localized prostate cancer multiple clones are detected.[143] Since the index lesion is generally thought to be the origin of metastatic disease, it is usually sampled for molecular testing; however, some evidence suggests that metastatic disease can also originate from minor lesions and approximately 20% of lymph node metastases derive from a nonindex lesion.[144] Intratumoral heterogeneity for DNA[68] and RNA[126,127] markers may therefore limit the prognostic utility of molecular testing due to sampling bias. Limited data suggest that commercially available RNA-based tests may vary in their sensitivity as a result of this molecular intratumoral heterogeneity.[126]

How Should Biomarkers With Purely Prognostic Implications Be Used?

As the progression of prostate cancer is driven by multiple factors, a single biomarker is not likely to provide sufficient information for clinical decision making. Like any clinical parameter, a prognostic biomarker should be used in conjunction with other parameters, including but not limited to patient comorbidities, PSA level, routine histopathology, and imaging findings, to make treatment decisions.

Utility and Generalizability of Prognostic Assays That Were Developed in a Non-CLIA Setting

Commercial tests use a multigene panel with an algorithm based on their expression levels to generate the test outcome measure. These proprietary algorithms are based on data from a large number of patients. Therefore, in-house testing of the same gene panel used by a commercial test would not necessarily be clinically useful. Some laboratories develop a generic multigene panel and only a proportion of the gene panel may represent a biomarker for prostate cancer prognosis. These panels may be used for general purposes, like typing of the carcinoma, but they should not be used for prognostication unless sufficiently validated on a large, clinically relevant patient population. Several molecular tests that are based on immunostaining for protein expression (for example, ERG and Ki-67) or in situ hybridization or next-generation sequencing for DNA aberrations (for example, *PTEN*) are available as CLIA-grade assays in pathology laboratories and may provide additional information or complement RNA-based tests.[145] However, data remain limited and relatively few comparative studies have been published. Inconsistencies and lack of correlation may be due to the different methods used or to preanalytical issues related to sample preparation. Lack of standardization in pathology laboratories for scoring of biomarker expression is an additional factor that currently limits this approach.

PATIENT AND CLINICIAN COMMUNICATION

A number of genomic tests are commercially available for men with localized prostate cancer who have undergone biopsy or radical prostatectomy and are faced with important decisions around treatment or observation/surveillance. The primary intent of biopsy-based molecular tests is to identify men with lower-risk prostate cancer who may benefit from active surveillance and thus avoid or delay treatment (typically surgery or radiation) and associated potential harms, while also identifying men who have higher-risk features for which treatment may be more appropriate. Overall, such tests may add meaningful value to existing laboratory and clinical parameters. In our literature review of such genomic tests, we found no

prospective, randomized studies of strategies with which to definitively prove clinical utility with clinically meaningful end points, and the vast majority of evidence was based on uncontrolled retrospective studies. Thus, whereas certain genomic tests are available and may be clinically informative in certain settings, the utility of routine or widespread ordering is discouraged, particularly since these tests are expensive.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[146]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care—and prostate cancer care—contribute significantly to this problem in the United States. Patients with cancer who are members of certain racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poor-quality care than other Americans.[147-152] Adoption of active surveillance in men with low-risk prostate cancer is significantly less in black versus white men in part because of socioeconomic and insurance factors.[153] However, early data suggest that genomic tests continue to predict aggressive disease in men with African American ancestry.[154-156] Additional studies focused on underrepresented populations are needed to better guide prostate cancer risk assessment and management. Patients may also lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform the treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs) —is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations and to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials the study selection criteria of which may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlights the importance of shared decision making regarding guideline use and implementation, particularly as it relates to estimated life expectancy and the often prolonged natural history of localized prostate cancer. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions and take these into account when formulating the management and follow-up plan.

For patients with prostate cancer younger than 65 years, the 10 most common comorbidities (in descending order) are hypertension, hyperlipidemia, diabetes, ischemic heart disease, anemia, arthritis, chronic kidney disease, depression, chronic obstructive pulmonary disease, and heart failure. For patients with prostate cancer older than 65 years, the 10 most common comorbidities (in descending order) are hypertension, hyperlipidemia, ischemic heart disease, anemia, diabetes, arthritis, chronic kidney disease, cataract, heart failure, and chronic obstructive pulmonary disease.

Accordingly, when there are significant competing health issues, prostate cancer management should be based on a systematic evaluation of health status using a screening tool, such as G8,[157] possibly combined with an assessment tool, such as gait speed, which has been shown to predict median life expectancy.[158] Reversible factors should be addressed before a final decision is made, but men with significant comorbidities resulting in a life expectancy of less than 10 years are highly unlikely to benefit from the use of these relatively expensive biomarkers.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[159,160] Higher patient out-of-pocket costs are a barrier to initiating and adhering to recommended cancer treatments.[161,162] Discussion of cost can be an important part of shared decision making and is often neglected.[163] Clinicians should discuss the use of less expensive alternatives when practical and feasible for the management of the patient's prostate cancer and there are two or more options that are comparable in terms of benefits and harms.[163] Patient out-of-pocket costs may vary depending on insurance coverage and, unfortunately, are not always easily attained or transparent. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should

be aware that different products may be preferred or covered by their particular insurance plan. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[163]

Cost implications are reported for the commercially available tests for the evaluation of patients with localized prostate cancer: Decipher, Onco*type* Dx, Prolaris, and ProMark. Cost effectiveness/implications of other tissue-based molecular tests for localized prostate cancer are beyond the scope of this guideline, although immunohistochemistry protein assays (eg, Ki-67) and single-gene in situ tests, such as fluorescence in situ hybridization (eg, PTEN), are considerably less expensive than genomic sequencing or gene expression panels—that is, in the range of hundreds versus thousands of dollars per assay.[164]

Commercially available transcriptome or protein-based panel tests take advantage of proprietary multiplexing platforms to simultaneously query the expression of multiple targets of interest. They make use of proprietary bioinformatic algorithms to formulate a probability risk score that is reported to clinicians and patients. Tests range in price from $3,900 to $5,150 (Table 3).

Prolaris uses biopsy tissue to evaluate disease aggressiveness based on expression of 46 genes involved in cell-cycle progression. Results predict the likelihood of a patient dying from prostate cancer within 10 years with watchful waiting (treatment typically initiated upon local or systemic symptoms rather than pathologic or biochemical progression). Onco*type* Dx Genomic Prostate Score queries the expression of 17 genes. The Genomic Prostate Score is bioinformatically inferred by combining expression results and clinical risk factors to predict the likelihood of a Grade Group 3 or greater or extracapsular extension (T3a) at radical prostatectomy. ProMark is a protein-based prognostic test that interrogates eight protein biomarkers by immunofluorescent multiplex staining of biopsy tissue sections and generates a risk score for adverse pathology (Grade Group $\geq$ 2 or stage $\geq$ T3b) that is reported back to the patient and treating physician. The Decipher Test evaluates 22 biomarkers to calculate a biopsy-based genomic risk score that predicts the 5-year probability of metastasis and a whole transcriptome analysis of the cancer along with a postprostatectomy test to estimate the risk of metastasis.

All tests are covered by Medicare for qualified patients and mentioned in the latest NCCN guidelines (v2.2019).[128] Financial assistance programs are offered by the companies for uninsured patients or those who cannot cover the cost in a single payment.

Cancer care costs are increasing and are often a substantial impediment and burden for patients. To ease this burden, tools have become available to help patients identify available resources, compare options, and be advised of payment assistance programs. The NCCN Reimbursement Resource App provides a vendor-neutral tool for patients to perform such comparisons on their own (https://www.nccn.org/apps/). In addition, several testing companies advertise financial subsidies, although general information is not readily disclosed on Web sites and may be patient specific.

In addition, studies are urgently needed to evaluate and compare the cost effectiveness of each of these tests. To date, there is a paucity of studies, with few such evaluations published.[165] One study using the Onco*type* Dx Genomic Prostate Score concluded that testing was cost effective in guiding treatment decisions, but was sensitive to narrow variations within certain parameters, which reinforced the importance of patient preferences in decision making. Similar studies have been reported for ProMark[166] and Prolaris.[167] Additional studies will be helpful in assessing and comparing cost effectiveness.

EXTERNAL REVIEW AND OPEN COMMENT

The draft guideline was sent to three clinicians (Daniel Spratt, MD; Martin Gleave, MD; and Charles Ryan, MD) external to both the writing group and the ASCO Genitourinary Cancer Guidelines Advisory Group for an external review. Main points raised were related to the ultimate utility of molecular and cellular biomarkers in this setting, given the lack of a predictive marker in prostate cancer, and their role in the context of the imaging modalities available and the clinical characteristics that determine each patient's risk group.

In addition to the external review process, from June 17, 2019, through to July 1, 2019, guideline recommendations were publicly posted online as part of an open comment process. A total of 14 respondents submitted their feedback. In general, respondents agreed with our draft recommendations as worded or with minor rewording suggestions, except for our draft recommendation 3, which had one respondent disagree on the basis of the ambiguity of interpretation, which resulted in a revision of our draft recommendation.

The Expert Panel considered all the feedback received in both the external review and the open comment in making their final revisions to this guideline.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation

Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and a summary in *Journal of Oncology Practice*.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

The challenge of assessing the biologic significance of newly diagnosed prostate cancers, as well as real-time measurement of serial changes over time in men whose disease is managed using active surveillance is rapidly moving beyond traditional measures of tumor grade and volume. Rapid developments in imaging technology, changes and variability of diagnostic strategies, and histopathology criteria defining biologic significance of a prostate cancer highlight the need for head-to-head comparisons to determine their individual and collective additive value. For example, several studies have demonstrated that gene expression profiles more accurately predict the presence of adverse pathology than MRI, even when the tumor is MRI visible.[30,112] While it has been shown that molecular testing increases the proportion of eligible men who choose and stay on surveillance, the impact on longer-term oncologic outcomes has not been demonstrated. Although the commercially available (US Food and Drug Administration–approved) tissue-based tests show strong and consistent prognostication, despite the limitation imposed by spatial tissue heterogeneity, whether the magnitude of improved prognostication justifies the cost of their routine use is open to discussion and will require longer-term follow-up to demonstrate both cost effectiveness and clinical utility in patient subsets.

We anticipate more biomarker-based tests will become available over time, including genetic, genomic, and epigenomic markers identified in tissue and body fluids. Furthermore, current guidelines for germline DNA testing in prostate cancer will likely be expanded and become a more significant factor in prostate cancer diagnostics, given the high level of heritability of the disease and downstream clinical implications.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

Patient-Clinician Communication[146] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

Clinically Localized Prostate Cancer[168] (http://ascopubs.org/doi/10.1200/JCO.18.00606)

Hypofractionated Radiation Therapy for Localized Prostate Cancer[169] (http://ascopubs.org/doi/10.1200/JCO.18.01097)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/genitourinary-cancer-guidelines.

EQUAL CONTRIBUTION

S.E.E. and H.B. were Expert Panel co-chairs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX

TABLE A1. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline Expert Panel

Name (and designation)	Affiliation/Institution	Role/Area of Expertise
Scott E. Eggener, MD (co-chair)	University of Chicago Medicine, Chicago, IL	Urology
Himisha Beltran, MD (co-chair)	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Neeraj Agarwal, MD	Huntsman Cancer Institute, University of Utah Health Care, Salt Lake City, UT	PGIN representative
Andrew J. Armstrong, MD	Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC	Medical oncology
Philip Cornford, MD	Royal Liverpool University Hospital, Liverpool, United Kingdom	Urology
Tony Crispino		Patient representative
Robert Benjamin Den, MD	Sidney Kimmel Medical College and Cancer Center at Thomas Jefferson University, Philadelphia, PA	Radiation oncology
David J. Grignon, MD	Indiana University School of Medicine, Indianapolis, IN	Pathology and laboratory medicine
Eric A. Klein, MD	Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH	Urology
Todd M. Morgan, MD	University of Michigan School of Medicine, Ann Arbor, MI	Urology
Alex J. Rai, PhD, DABCC, FACB	Columbia University Irving Medical Center, New York, NY	Pathology and laboratory medicine
T. van der Kwast, MD, PhD	Princess Margaret Cancer Center, University Health Network, Toronto, Ontario, Canada	Pathology
R. Bryan Rumble, MSc	American Society of Clinical Oncology, Alexandria, VA	Staff/health research methodologist