Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline

Eggener et al.
Introduction

- At diagnosis of prostate cancer, there is a diverse spectrum of clinical course ranging 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.

- 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 quality of care.

- The purpose of this clinical practice guideline is to provide recommendations to physicians (including medical oncologists, radiation oncologists, and urologists), other health care practitioners (e.g. nurses, nurse practitioners, physician assistants), patients, and caregivers based on best available evidence regarding the role of molecular, cellular, and genomic biomarkers in localized prostate cancer.
ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

• a systematic literature review by ASCO guidelines staff
• an expert panel provides critical review and evidence interpretation to inform guideline recommendations
• final guideline approval by ASCO CPGC

The full ASCO Guideline methodology manual can be found at:

www.asco.org/guideline-methodology
Clinical Questions

This clinical practice guideline addresses four overarching clinical questions:

1) Are there molecular prostate cancer biomarkers to identify patients most likely to benefit from active surveillance?

2) Are there molecular biomarkers to diagnose clinically significant prostate cancer?

3) Are there molecular biomarkers to guide the decision of post-prostatectomy adjuvant versus salvage radiation?

4) What are comparative strengths/weakness of genomics vs MRI in identifying clinically significant prostate cancer?
Target Population and Audience

Target Population
Men with localized prostate cancer.

Target Audience
Medical oncologists, radiation oncologists, urologists, other health care practitioners, patients, and caregivers.
Summary of 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 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 where the assay result, when considered as a whole with routine clinical factors, is likely to impact 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. While testing may influence management decisions, there is not high-level evidence 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.
Summary of Recommendations

CLINICAL QUESTION 1
Are there molecular biomarkers to identify prostate cancer patients most likely to benefit from active surveillance?

Recommendation 1.1.
Commercially available molecular biomarkers (i.e., Oncotype Dx Prostate, Prolaris, Decipher, ProMark) may be offered in situations where the assay result, when considered as a whole with routine clinical factors, is likely to impact 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, thus should not be offered. (Type: Evidence-based; Evidence quality: Insufficient; Strength of recommendation: Moderate)
Summary of Recommendations

CLINICAL QUESTION 2
Are there molecular biomarkers to diagnose clinically significant prostate cancer?

Recommendation 2.1.
Commercially available molecular biomarkers (i.e., Oncotype Dx Prostate, Prolaris, Decipher, ProMark) may be offered in situations where the assay result, when considered as a whole with routine clinical factors, is likely to impact 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, thus should not be offered. (Type: Evidence-based; Evidence quality: Insufficient; Strength of recommendation: Moderate)
Summary of Recommendations

CLINICAL QUESTION 3
Are there molecular biomarkers to guide the decision of post-prostatectomy adjuvant versus salvage radiation?

Recommendation 3.1.
The Expert Panel recommends consideration of a commercially available molecular biomarker (e.g., Decipher Genomic Classifier) in situations where the assay result, when considered as a whole with routine clinical factors, is likely to impact management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the post-prostatectomy 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, thus should not be offered. (Type: Evidence-based; Evidence quality: Insufficient; Strength of recommendation: Moderate)
Summary of Recommendations

CLINICAL QUESTION 4.
What are the comparative strengths/weakness of genomics versus MRI in identifying clinically significant prostate cancer?

Recommendation 4.
In men with newly diagnosed prostate cancer eligible for active surveillance, both MRI and genomics intend to identify clinically significant cancers. The Expert Panel endorses their use only in situations where the result, when considered with routine clinical factors, is likely to impact management. This may include, for instance, in the initial management of men 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).
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 outcome across patients.

- Molecular, cellular, and genomic information have the potential to improve upon clinical criteria by providing unique insights into underlying tumor biology such as cellular proliferation, differentiation, androgen receptor signaling, as well as identifying unique vulnerabilities that may affect local or systemic treatment response.

- Despite the promise of molecular biomarkers in addressing important clinical unmet needs, there is currently insufficient evidence to recommend 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.
Special Commentary

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

1) What are optimal approaches for tumor selection and processing for molecular testing?

2) How to interpret assay characteristics (e.g. reproducibility, quality of tissue, tumor heterogeneity)?

3) How should biomarkers with purely prognostic implications be used?

4) What is the utility and generalizability of prognostic assays developed in a non-Clinical Laboratory Improvement Amendments (CLIA) setting?

Refer to the full text of the guideline for these topics.
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 the 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.

While 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.
Cost Implications

- Cost implications are reported for the commercially available tests for evaluation of patients with localized prostate cancer: Decipher, Oncotype Dx, Prolaris, and ProMark.

- Cost effectiveness/implications of other tissue-based molecular tests for localized prostate cancer are beyond the scope of this guideline, though immunohistochemistry protein assays (e.g. Ki67) and single gene *in situ* tests such as FISH (e.g. PTEN) are considerably less expensive than genomic sequencing or gene expression panels (i.e. in range of hundreds versus thousands of dollars per assay).

- Studies are urgently needed to evaluate and compare the cost effectiveness of each of these tests.
Limitation of the Research and Future Research

- The challenge of assessing the biological significance of newly diagnosed prostate cancers, as well as real-time measurement of serial changes over time in men managed by 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.

- We anticipate more biomarker-based tests will become available over time, including genetic, genomic and epigenomic markers identified in tissue and body fluids.

- Further, the current guidelines for germline DNA testing in prostate cancer will likely be expanded in the future and become a more significant factor in prostate cancer diagnostics given the high level of heritability of the disease and downstream clinical implications.
Additional Resources

More information, including a Data Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/genitourinary-cancer-guidelines

Patient information is available at www.cancer.net
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