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Molecular Biomarker Testing in Localized Prostate Cancer

The Critical Role of Pathologists

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The American Society of Clinical Oncology (ASCO) recently issued the guideline Molecular Biomarkers in Localized Prostate Cancer,[1] which was published in the *Journal of Clinical Oncology* and endorsed by the College of American Pathologists. We want to highlight a few specific issues with direct relevance to pathologists. Our goals in this article are 3-fold. First, we aim to summarize the key points from the ASCO guideline, with a particular emphasis on implications for practicing pathologists and select scenarios when biomarker testing may be appropriate for patients with localized prostate cancer. Second, we will review the commonly used biomarker assays, including their testing methodology and intended clinical utility. Finally, we will highlight the critical role of pathologists in selecting appropriate tissue for testing and in communicating with clinical colleagues to ensure these tests are requested properly.

Patients with localized prostate cancer and their oncologists are faced with numerous difficult decisions regarding strategies for follow-up and surveillance, options for definitive management, and/or selection of adjuvant local or systemic therapy if surgery is performed. A variety of important traditional clinical, radiologic, biochemical, and histopathologic parameters (ie, Gleason score/Grade Group, tumor extent) must be integrated in a holistic fashion for each individual patient, and a personalized approach considering each patient's goals and prognosis is essential. In recent years, several biomarker assays have become available for patients with localized prostate cancer, all with the goal of offering additional predictive insight into the biology of the patient's tumor beyond what is provided by the aforementioned established clinicopathologic parameters. Given that these assays are relatively new but widely available, and associated with significant costs, the ASCO expert panel recognized that patients and oncologists would benefit from evidence-based recommendations to evaluate when such tests may provide clinical benefit for patients with localized prostate cancer.

The ASCO expert panel framed its recommendations around 4 key clinical questions and evaluated 109 relevant publications to inform them. Specifically, the panel sought to determine if currently available biomarker assays are capable of: (1) identifying patients most likely to benefit from active surveillance, (2) diagnosing clinically significant prostate cancer, (3) guiding the decision between post-prostatectomy adjuvant versus salvage radiation, and (4) surpassing the capability of magnetic resonance imaging to identify clinically significant prostate cancer. For all 4 questions, the conclusion based on review of the available evidence was essentially the same—at the current time, there are no high-quality, prospective studies that support the routine use of biomarker assays to address these questions. However, the guideline asserts that molecular biomarker assays may be of value in select circumstances when the appropriate clinical management is not entirely clear based on the available clinicopathologic parameters. The panel repeatedly emphasized that regarding all 4 clinical questions, biomarker testing should only be pursued in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to have an impact on patient management.[1] Specific scenarios with sufficient clinicopathologic ambiguity to merit biomarker testing are offered. For example, biomarker assays may be helpful for a patient whose biopsies demonstrate a low volume, Gleason score $3 + 4 = 7$ prostate cancer who is considering active surveillance. Assay results indicative of aggressive tumor biology could alter management by swaying decision-making toward definitive therapy versus active surveillance (or vice versa). In contrast, for a patient with prostate biopsies demonstrating a significant volume of high-grade prostate cancer, definitive surgical or radiation therapy would most likely be recommended, and thus biomarker testing would not alter clinical decision-making and would not be appropriate.

It is not only critical for pathologists to appreciate when biomarker testing may be appropriate, but also to recognize how these tests are performed, and the specific questions

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As representatives and members of the College of American Pathologists (CAP) Center Guideline Committee.

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they are intended to answer. Thus, we will briefly review the commercially available assays, with a particular emphasis on clinicopathologic considerations. Decipher Prostate Biopsy and Decipher Prostate RP (Decipher Biosciences, San Diego, California) use formalin-fixed, paraffin embedded (FFPE) tissue from core biopsy or radical prostatectomy specimens, respectively. Both assays measure expression levels of 22 mRNA transcripts to compute a risk score from 0.0 to 1.0 and produce estimated risks of 5-year metastasis and 10-year mortality from prostate cancer. In addition, the postoperative radiation therapy outcomes score can be determined to predict responsiveness to adjuvant radiation therapy.[2] The Decipher Prostate RP assay is specifically intended for patients with adverse pathologic features at radical prostatectomy, including positive surgical margin, or with pT3 disease such that adjuvant radiation may be considered. Such testing is therefore not generally appropriate for patients lacking these adverse features, although biochemical recurrence after prostatectomy is also a possible indication for testing. In addition, the Decipher Prostate Biopsy assay quotes a risk of identifying high-grade prostate cancer (designated Grade Group $\geq$3) at radical prostatectomy. Thus, in biopsy cases already harboring Grade Group $\geq$3 carcinoma, this assay is unlikely to alter management and would lack clinical benefit.

The Oncotype DX Genomic Prostate Score assay (Genomic Health Inc, Redwood City, California) produces a score from 0 to 100 based on levels of 17 mRNA transcripts quantified from FFPE prostate biopsy tissue.[3] Reports offer risk assessment of prostate cancer metastasis and mortality at 10 years, as well as risk of adverse pathologic features at radical prostatectomy, including likelihood of pT3 or Grade Group $\geq$3 tumor. Thus, it stands to reason that patients with a biopsy diagnosis of Grade Group $\geq$3 carcinoma, or with extraprostatic extension, would not benefit from this assay, because such patients are not generally considered candidates for active surveillance.

The Prolaris biopsy assay (Myriad Genetic Laboratories, Salt Lake City, Utah) produces an overall risk score based on mRNA expression of cell cycle genes,[4] which is subsequently integrated with clinicopathologic features, such as age, prostate-specific antigen, and Gleason score to estimate risk of prostate cancer metastasis and mortality at 10 years. Separate risk estimates are quoted for patients considering active surveillance and are compared to estimated risks if primary radiation or prostatectomy is pursued. The Prolaris assay can also be performed on prostatectomy tissue to estimate the 10-year risk of biochemical recurrence.

In contrast to the previously described assays, the ProMark assay (Metamark Genetics Inc, Waltham, Massachusetts) is based on automated image analysis of quantitative immunofluorescence for 8 proteins and is performed directly on submitted biopsy tissue.[5] A score from 0 to 100 is reported, which estimates risk of various adverse pathology features at radical prostatectomy, including pT3 disease, Grade Group $\geq$3 or higher histopathology, or lymph node metastasis. The test is specifically designed to assess only biopsies with Grade Group 1 or 2 carcinoma, and therefore analysis of biopsies containing higher-grade tumor would not be indicated.

It is essential to recognize that for all of the above assays, certain preanalytic or histopathologic factors may preclude a meaningful analysis. Specifically, these assays are only validated on either biopsy or prostatectomy FFPE specimens containing untreated prostatic acinar adenocarcinoma. Therefore, tumors that have been exposed to radiation or hormonal therapy should not be submitted for these assays, nor should specimens that were previously frozen or not fixed in formalin. Importantly, these assays would also not be appropriate for nonacinar variants of prostate carcinoma, nor would they be appropriate for other tumor types involving the prostate, such as urothelial carcinoma. If a biopsy has multiple specimens positive for carcinoma, pathologists should choose the most representative specimen, usually the one with the highest-grade group, or largest tumor volume, for testing. Pathologists should also make sure there is sufficient tumor in the tissue submitted for testing. Furthermore, we emphasize that the commercially available assays discussed in the guideline are not the only biomarker assays that may be informative and clinically relevant for patients with localized prostate cancer. Laboratory-developed tests, including sequencing-based genetic panels, and/or immunohistochemical or fluorescence in situ hybridization–based assays may be equally informative and potentially more cost-effective for a given patient than the commercial assays exclusively referenced in the guideline.

In summary, we commend the ASCO expert panel for conducting a thorough literature review and agree with its overall conclusion that at the present time, molecular biomarker testing for localized prostate cancer patients is not warranted on a routine basis; readily available and well-established clinical, radiologic, biochemical, and pathologic factors are sufficient for guiding clinical management for a substantial percentage of patients. In cases occupying clinicopathologic gray areas, for which biomarker testing is deemed likely to change clinical management, we want to highlight the critical role of the pathologist in selecting adequate, optimal tissue for testing, which is essential for providing clinically relevant and cost-effective biomarker testing for patients with localized prostate cancer. Finally, we underscore the importance of scrutinizing both the capabilities and limitations of a given assay before relying on its output for clinical decision-making.

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