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Integrating the Genomic Prostate Score into Clinical Practice Workflow

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Abstract

Introduction: A dilemma that urologists face is how to determine which patients with prostate cancer need immediate intervention and which patients can be safely placed on active surveillance. Gene expression profile analysis of biopsy tissue has been proposed as a means of providing more accurate risk stratification for low risk prostate cancer. However, there is a general lack of acceptance and standardization around the integration of genomic testing in clinical practice. The Oncotype DX® prostate cancer assay is a commercially available tissue based assay that assesses the expression of key genes across multiple biological pathways predictive of prostate cancer aggressiveness from the diagnostic biopsy specimen, and reports an individual Genomic Prostate Score.

Methods: With the recommendations set forth in this article we aim to standardize operational best practices for the integration of the Genomic Prostate Score into clinical practice. Its purpose is to provide practical guidance to help physicians understand, run, interpret and communicate actionable results to patients.

Results: The Genomic Prostate Score reflects the biology of the underlying tumor to help guide initial treatment decisions at the time of biopsy. This article is based on real-world evidence from the authors' respective experiences at their institutions and practices. The authors were carefully selected based on their depth of experience and knowledge about the Genomic Prostate Score and, as such, it is their expertise that is being leveraged to support the best practices algorithm.

Conclusions: This article provides easy to use, clear-cut and practical guidance for physicians on how to use the Genomic Prostate Score to inform decisions regarding active surveillance.

Key Words: prostatic neoplasms, genomics, biological assay

Abbreviations and Acronyms

AS = active surveillance

GPS = Genomic Prostate Score

NCCN® = National Comprehensive Cancer Network®

PCa = prostate cancer

PSA = prostate specific antigen

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Differentiating indolent from aggressive PCa can be difficult and consequently lead to overtreatment.[1,2] Recent controversies and confusion about PSA screening have highlighted the unmet need for improved decision making tools for men with localized PCa.[3] Although screening has resulted in a decrease in PCa mortality, it is clear that these gains have come at the cost of diagnosing and treating many men with indolent PCa, cancers with a very low probability of progressing and becoming lethal. There is now strong evidence from multiple studies that low risk disease can be safely managed with active surveillance, a strategy involving careful monitoring with serial PSA measurements, examinations and biopsies, with curative intervention offered to those men with evidence of disease progression. Molecular markers of tumor aggressiveness can improve the risk assessment of PCa,[4] thereby helping to identify which patients may not need immediate treatment with surgery or radiation.

The viability of AS as an initial strategy for men with low risk disease has now been recognized by societies in their guidelines, including those of the American Urological Association, European Association of Urology and NCCN. Despite this recognition and the evidence, AS remains underused, largely due to concerns about the accuracy of existing risk stratification tools available at biopsy (especially given the issues of prostate tumor heterogeneity and the potential for under sampling by conventional biopsy approaches).

Several groups have studied AS outcomes across a variety of cohorts. Although each of these cohorts enrolled or selected men with favorable risk profiles, there were differences in patient selection, ie Gleason 3+3 and 3+4, as well as differences in surveillance protocols and triggers for intervention. Despite these differences, AS has been shown to be exceedingly safe, with a reported median followup of approximately 40 months and a PCa specific survival greater than 99%.

Although we rely on risk stratification to identify men who have low risk features, 30% to 40% of men undergoing radical prostatectomy for presumed low risk disease will have higher grade, higher stage disease or both on pathological staging. Current tools used in prostate cancer staging and risk stratification (PSA, Gleason score, tumor stage) have limitations. Combining current tools with genomic information will improve risk stratification and the accuracy needed for decision making. Given the uncertainty of current risk stratification, it is not surprising that a majority of men today receive immediate therapy.

Oncotype DX

The development strategy for the Oncotype DX PCa assay (which provides a more accurate and individualized risk assessment for men at the time of PCa diagnosis) was based on the successful approach used to develop the Oncotype DX breast and colon cancer assays. Two challenges faced in developing the test were 1) addressing issues of tumor heterogeneity and multifocality, and 2) optimizing a technology platform to reliably analyze and provide a GPS result based on the small amounts of tumor typically found in prostate needle biopsies.[5]

Oncotype DX is a 17-gene expression assay that has been analytically validated using limited RNA inputs.[5] The assay consists of 5 reference genes (which account for varying RNA quality/quantity) and 12 cancer related genes representing 4 distinct biological pathways (androgen signaling, stromal response, cellular organization and proliferation). These contribute to the predictive value of the assay. The assay provides a GPS, which ranges from 0 to 100, with higher scores representing less favorable pathology and lower scores representing more favorable pathology. The GPS is calculated by summing the weighted expression of genes associated with worse outcomes and subtracting the weighted expression of genes associated with better outcomes.

The assay has been clinically validated in 2 separate independent cohorts confirming Oncotype DX as a predictor of the likelihood of adverse pathology from the prostate needle biopsy and also as a predictor of the risk of biochemical recurrence after surgery.[6,7] The test was validated in patients with NCCN very low, low and a subset of intermediate risk disease referred to as low-intermediate risk (Gleason 3+4 disease). The test has not been studied in higher risk patients and, therefore, should not be considered in that setting.

The intention of the GPS is to be used with accepted clinical criteria (ie NCCN risk classification) to stratify biopsy diagnosed localized PCa according to biological aggressiveness and, thus, direct patient care. Beyond simply refining risk categorization for a patient, the value of the GPS lies in its ability to provide actionable information to support treatment decisions for patients with very low, low and low-intermediate risk disease. The GPS provides individual risk estimation based on the likelihood of favorable pathology, meaning a low Gleason grade and organ confined disease. The report also breaks out the elements of adverse pathology and notes separately the risk of high grade disease and risk of high stage disease. The cases shown in figure 1 demonstrate how the GPS can provide actionable feedback impacting treatment decisions. For some clinicians in certain clinical settings these individual components may be informative for treatment planning. We believe a standard approach to integrating Oncotype DX into clinical practice is warranted (fig. 2).