New Genetic Markers for Prostate Cancer

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KEYWORDS

• Prostate cancer • Gene expression testing • Biomarker

KEY POINTS

- Novel gene-based tests have been developed to improve the prediction accuracy at various phases within the prostate cancer (PCa) disease course.
- Urine-based assays evaluating the expression levels of PCA3 and TMPRSS2:ERG aim to refine the selection for both initial and repeat prostate biopsy.
- Tissue-based gene expression tests have been developed to predict the occurrence of subsequent PCa events, including adverse characteristics, biochemical recurrence, metastatic progression, and PCa mortality.

INTRODUCTION

From a global perspective, prostate cancer (PCa) is a public health burden, detected in approximately 899,000 men per year and culminating in 258,000 deaths.[1] As a consequence of early detection resulting from population-based screening efforts, vigilant primary treatment, and the integration of advanced therapies in late-stage disease, declines in PCa mortality have been observed.[2] Yet as a highly prevalent malignancy with considerable variation in aggressiveness and an array of treatment options at numerous decision points within the disease, a need has emerged for increasingly reliable tools with which patients and clinicians alike may better predict the likelihood of downstream outcomes.[3] Such developments hold potential for informing accurate management decisions and may facilitate a reduction of both over and undertreatment. On this front, genomic characterization may provide prognostic insights not presently offered with other tools and may assist in the allocation of aggressive therapy for individuals at higher risk, while reducing the treatment burden for individuals less likely to derive benefit.

Conventional clinical stratification tools for PCa offer favorable delineation of downstream end points but will mistakenly categorize a proportion of patients as either higher or lower risk of experiencing a given disease-related event. Such information may be mobilized to assist in the selection of initial management strategy, increasingly rendered as initial definitive therapy or active surveillance.[4] Similarly, following primary treatment, prediction of the risk of failure is useful in determining the potential value of adjuvant or salvage therapy.[5,6] At initial diagnosis, instruments incorporating standard variables, including age, prostate-specific antigen (PSA), Gleason score, tumor volume, and clinical stage, estimate the risk of disease recurrence following treatment, including biochemical recurrence, metastases, and cancer-related mortality and overall mortality with accuracies in the range of 60% to 80%.[7–9] Uncertainty in these predictions may be a source of distress for patients and physicians and may also inform misdirected management decisions: intervention for biologically indolent tumors or, conversely, unwitting missed opportunities for intervention among those harboring insidious disease.[3,10]

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On the heels of insights gained into PCa biology and technological advancements affording accessible, high throughput sequencing, assays have emerged that evaluate numerous junctures within the PCa disease process.[11] Spanning the prediagnostic, initial detection and posttreatment settings, this expanding battery of risk-stratification tools seek to offer improved assessment of outcome and gain widespread implementation in clinical practice. In light of the novelty of such developments, the authors aim to critically review the current body of tools that have appeared in recent years and the details of their supporting evidence and offer a contextualization of the pipeline of emerging tests under development.

PRINCIPLES OF DESIGN AND EVALUATION

Phases of Critical Evaluation

The evidence in support of an emerging prognostic genetic marker is established on several accounts addressing reproducibility and clinical performance. Although assays developed in a research setting may seem to offer reliability in measurement, it is essential that any gene-based test intended for widespread clinical utilization exhibit consistency when implemented in large-scale commercial laboratories.[12] Initial *analytical validation studies* address the ability of an assay to consistently measure a biological event within the context of a clinical laboratory. These studies yield valuable information relating to the variation that exists among clinical specimens.[13] Measures to ensure the quality and consistency of commercially available assays fall within the rubric of the Clinical Laboratory Improvement Amendment (CLIA) under the auspices of the Centers for Medicare and Medicaid Services. As the gene expression–based assays are increasingly used to inform clinical decision making, CLIA certification often serves as a valuable analytical standard.

Clinical validation studies address the relationship between the test and a prespecified clinical outcomes. In the setting of PCa, these end points may vary by tissue source and the proposed event of interest and often include adverse pathology, biochemical recurrence (BCR), progression to metastatic disease, or PCa-specific mortality (PCSM). Clinical validation studies often use archival, paraffin-embedded tissue of patients with extended follow. As a consequence, it is critical to note whether such retrospectively conceived studies adhere to blinded evaluation design, if specimens were collected in a standardized and prospective fashion, and whether the disease characteristics of the study populations remain valid today. Such measures act to minimize potential sources of bias in the selection of study subjects that may undermine the integrity and conclusions.[14]

TESTS BEFORE DIAGNOSIS

Most PCa detected worldwide are the result of biopsy undertaken in the setting of elevated PSA. Owing to the well-recognized deficiencies in specificity of PSA for the identification of clinically significant disease, a considerable number of individuals will undergo screening and biopsy to detect a single high-risk cancer.[15] The development of accurate markers to better select those at greatest risk for harboring significant and actionable disease would, therefore, be impactful for men who may be spared unneeded biopsy or detection of low-grade tumors in whom treatment may offer little benefit to longevity or quality of life. In this setting, new markers have emerged that seek to offer improvements in the selection for initial or repeat biopsy.

URINARY-BASED GENE EXPRESSION ASSAYS

Prostate Cancer Antigen 3

Urine-based PCa assays have been regarded as a promising means for the acquisition of markers highly specific to the prostate. Measurement of PCa antigen 3 (PCA3) mRNA expression within post–digital-rectal-examination (DRE) urine has been evaluated as a predictor for the detection of PCa on subsequent biopsy whereby higher expression levels have been associated with PCa discovery.[16] A urinary PCA3 assay (Progensa, Hologic Inc, Bedford, MA) is currently approved by the Food and Drug Administration in the setting of prior negative biopsy, where studies have examined the predictive value of using PCA3 thresholds for selecting men for repeat biopsy.[17] Among men with a minimum of one negative biopsy, the area under the receiver operating characteristic (AUROC) curve for PCa detection has ranged from 0.651 to 0.684; at a cutoff of 35, the sensitivity and specificity has ranged from 54% to 58% and 72% to 74%, respectively.[18–20] In the biopsy-naïve setting, PCA3 expression levels have been evaluated in several studies, including men with elevated PSA levels in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) as well as in a prospective multicentered study of men using the Progensa PCA3 assay. At a PCA3 cutoff level of 35 or greater, the sensitivity and specificity for PCa detection ranged from 64% to 68% and 55.7% to 76.0%, respectively, and outperformed