An overview of biomarkers in the diagnosis and management of prostate cancer

Alex Uhr, MD, Lydia Glick, BS, Leonard G. Gomella, MD
Department of Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

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Introduction: *Prostate cancer is a common malignancy with highly variable clinical presentation and outcomes. Diagnosis and management remain a challenge and at times become highly controversial. Novel biomarker assays have shown promise as an adjunctive tool to aid in patient shared decision-making, risk stratification, and disease management. This presentation at the 2020 Jefferson Urology Symposium provided a review of current commonly used biomarkers for prostate cancer.*
Materials and methods: *We reviewed the current literature on the use of biomarkers in the diagnosis and treatment decisions in localized prostate cancer.*
Results: *Biomarker assays were reviewed and presented according to clinical application of each test. In the consideration of initial prostate biopsy the blood tests for PHI, and 4K Score, and urine tests PCA3, Select MDx and ExoDx are available. In the consideration of treatment versus active surveillance in the biopsy positive setting OncotypeDx, Prolaris and Decipher are available. In patients with an initial negative biopsy, 4K score, PCA3, ExoDx and the tissue biopsy based Confirm MDx assay can help guide the decision to perform repeat biopsy. In the consideration for adjuvant radiation following radical prostatectomy the most extensive literature available supports the use of Prolaris or Decipher tissue assays.*
Conclusions: *With the significant burden of men being diagnosed with prostate cancer, it is desirable to appropriately risk stratify patients to avoid unnecessary biopsies and over-treatment in low risk patients and guide appropriate treatment strategies in high risk patients. Selected biomarkers presented are useful adjunctive precision medicine tools to aid in shared decision making and to direct treatment decisions.*

Key Words: prostate cancer, biomarkers, genomics, precision medicine, active surveillance

Introduction

Prostate cancer is the second most common solid tumor cancer and the most frequent urologic malignancy in men worldwide. In 2020 it is estimated that in the United States 191,000 men will be diagnosed and approximately 33,000 men will die from the disease. It accounted for 26% of all new cancer cases in men in the United Kingdom in 2017.[1,2] The application of prostate-specific antigen (PSA) based screening has led to an increase in men undergoing prostate biopsy and has provided the opportunity for early cancer diagnoses with the risk of unnecessary biopsy resulting in over diagnosis of clinically unimportant disease.[3,4] With the widespread prevalence of prostate cancer, it is important to distinguish between patients with clinically significant cancers that require treatment and those who may be candidates for less aggressive active surveillance and avoid unnecessary treatment. While men with higher Gleason scores have been shown to have higher mortality rates, men with low risk disease have about a 3% mortality rate at 15 years after diagnosis. In patients with low risk disease who have a non-aggressive cancer, there is potential for over-treatment, often with significant, life altering side effects.[5,6] In patients who underwent radical prostatectomy, it has been reported in the literature that up to 90% of patients experienced some degree of erectile dysfunction and more than 50% reported incontinence.[7] Because of the heterogenous nature of prostate cancer, correctly identifying patients through precision medicine strategies who may be at risk for aggressive disease as well as those with indolent disease in order to guide the best management is essential.

Current clinical tools used to manage prostate cancer typically includes PSA levels, digital rectal exam (DRE) abnormalities, imaging data, age coupled with

Address correspondence to Dr. Leonard G. Gomella, Department of Urology, Kimmel Cancer Center, Thomas Jefferson University, 1025 Walnut Street, Suite 1100, Philadelphia, PA 19107 USA

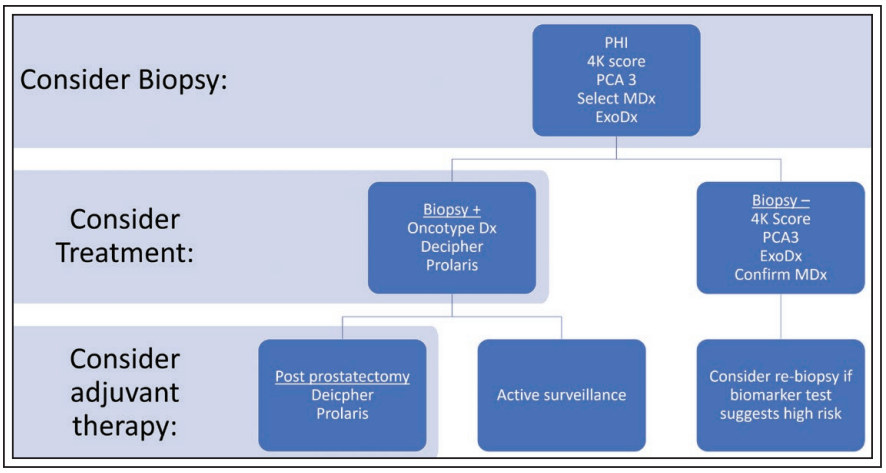

Figure 1. Clinical applications of some commonly used biomarkers in prostate cancer.

overall health and life expectancy, ethnicity, genetic predisposition and pathologic tumor characteristics. In men with elevated PSA > 4 ng/mL, up to 75% will have a negative prostate biopsy. Over the last few years biomarker testing has become popular as supplemental tools to aid in decision-making. The use of prostate cancer molecular biomarker analysis of the tumor is now included in guidelines such as in the National Comprehensive Cancer Network (NCCN) for risk stratification and staging of localized disease. A variety of molecular based tests are commercially available that may provide useful adjunctive information at various stages in the prostate cancer pathway including diagnosis, primary treatment or adjuvant therapy. The presentation, summarized here, provided a basic overview of the biomarker tests that are currently available, stratified by indication for each specific test, Figure 1.

For patients with clinical suspicion of prostate cancer who are considering biopsy

Prostate Health Index (PHI) (Beckman Coulter, Brea, California, USA) score is an FDA approved blood test that takes into account multiple proteins including PSA, free PSA and pro2PSA in a single formulated value that is more specific for prostate cancer than PSA alone. It is indicated for men with no prior biopsy who have a PSA between 4-10 ng/mL and non-suspicious DRE. It has been associated with both the presence of prostate cancer on biopsy, and a Gleason score of 4+3 or greater. It also reduces the rate of negative biopsy. PHI is reported in one of four categories correlating with increased probability of cancer.[8,9]

4K score (OPKO Health, Elmwood Park, New Jersey, USA) is a blood based test that considers 4 kallikreins (total PSA, free PSA, intact PSA, hK2) as well as clinical information (age, DRE, prior biopsy results) in an algorithm to predict aggressive prostate cancer. It is reported as a percentage of having Gleason ≥ 7 disease. It also stratifies the 20 year risk of developing metastatic disease and prostate cancer mortality. It is indicated in men considering initial biopsy or those with prior negative biopsy with ongoing clinical suspicion of cancer.[10]

Progensa Prostate cancer gene 3 (PCA3) (Hologic, Marlborough, Massachusetts, USA) is a urine based biomarker collected after DRE for use in men with suspected prostate cancer before initial biopsy or after prior negative biopsy. PCA3 is a prostate specific protein not expressed in other tissues or cancers, and is overexpressed by prostate cancer cells. Unlike PSA, it is unrelated to overall prostate size, and unchanged by 5 alpha-reductase inhibitor status. It has been suggested that for biopsy naïve patients, PCA3 > 60 increases likelihood that cancer will be detected, and a value < 20 has a high negative predictive value for cancer presence.[11-15]

Select MDx (MDxHealth, Irvine, California, USA) is a non-invasive urine methylation assay for biopsy naïve men with an elevated PSA and/or DRE that produces a likelihood of detecting prostate cancer on biopsy (illustrated by a percentage). It measures urinary mRNA levels of HOXC6 and DLX1 proteins; higher levels are associated with increased probability of having aggressive cancer. This test predicts Gleason ≥ 7 disease with 98% negative predictive value (NPV) and Gleason ≥ 8 disease with 99% NPV and has been shown to reduce the number of unnecessary biopsies by up to 53%.[3]

ExoDx IntelliScore (Exosome Diagnostics, Cambridge, Massachusetts, USA) is a validated urine test in men over 50 years old who are scheduled for initial prostate biopsy with PSA levels 2-10 ng/mL to predict the likelihood of harboring grade group 2 or greater cancer. It is a standalone result calculated solely from exosome gene expression with exclusion of clinical parameters to produce a low or high risk score. Using a validated pre-determined cut off point of 15.6, the test has a negative predictive value > 90%, and a sensitivity of 92%.[16]

Confirm MDx (MDxHealth, Irvine, California, USA) is a non-invasive test that relies on archival on prior negative prostate biopsy specimens collected within the past 30 months in patients with persistent abnormal PSA who are considering a repeat biopsy. It uses a three-gene (*GSTP1*, *APC*, and *RASSF*) PCR assay to identify an epigenetic field surrounding cancer cells and map DNA methylation which may help guide future biopsy targets. A positive result provides risk prediction for Gleason ≥ 7 disease. A negative result with no areas of DNA methylation corresponds with a 96% NPV for Gleason ≥ 7 disease and 90% NPV for all prostate cancer.[17,18]

For patients with biopsy proven prostate cancer considering active surveillance or treatment, or post prostatectomy patients considering adjuvant therapy

Oncotype DX - Genomic Prostate Score (GPS) (Genomic Health Inc., Redwood City, California, USA) is a non-invasive test on biopsy tissue used to identify the aggressiveness of disease and provide a personalized risk assessment in NCCN-defined very low risk, low risk, and intermediate risk cancer patients. The assay predicts tumor aggressiveness based on 17 gene panel (12 prostate cancer related genes and 5 housekeeping controls) within cellular communication pathways including androgen signaling, stromal response, and cellular organization and proliferation stages. Results are reported as a GPS score from 0-100 where higher scores correlate with higher risk of aggressive disease. Risk of adverse pathology (Gleason > 4+3 and/or pT3+), metastatic disease and prostate cancer death at 10 years is also predicted.[19]

Decipher (GenomeDx Biosciences, Vancouver, BC, Canada) is a genome wide test reflecting multiple biological pathways in patients with NCCN-categorized very low, low, or favorable intermediate risk cancer after a positive biopsy. It is reported as a continuum risk score from 0-1 and is independent of clinical or pathological features. It predicts the likelihood of high grade disease, 5 year metastasis, and 10 year cancer specific mortality. It has also been shown to be an independent predictor of adverse pathology and metastasis. Decipher can be performed on post radical prostatectomy specimens and is useful in patients who have adverse pathology (pT3 disease, positive surgical margins) or biochemical persistence/recurrence to help identify patients likely to benefit from adjuvant or salvage radiation. In patients with a risk score ≥ 0.4, there was a 6% versus 23% incidence of metastatic disease at 5 years after adjuvant versus salvage radiation.[20,21,22]

Prolaris (Myriad Genetics, Salt Lake City, Utah, USA) is also a tissue biopsy based test that combines RNA expression of 46 genes (31 cell cycle progression genes and 15 housekeeping controls) with clinical and pathologic features to stratify 10 year risk of metastasis after definitive treatment and disease specific mortality if managed conservatively. This test can also be useful in post prostatectomy specimens to predict 10 year risk of biochemical recurrence to help identify patients who may benefit most from adjuvant therapy.[23]

For patients with advanced disease and in the decision for systemic therapies**

AR-V7 (Genomic Health Inc., Redwood City, California, USA) is a blood-based test useful in patients with metastatic castrate-resistant prostate cancer who have previously or are currently on androgen-receptor (AR) targeted medications to help determine appropriate future systemic therapy. AR-V7 is a truncated AR circulating tumor cells that is activated independent of androgen binding, and may be present in men with previous or current AR targeted therapy. AR-V7 positive patients have poor response to AR blockade, and therefor may benefit more from chemotherapy or other non-androgen pathway therapies. In contrast, AR-V7 negative patients may respond to all therapeutic agents.[24,25]

Conclusion

Prostate cancer can be a highly variable and heterogeneous disease, making diagnosis, prognosis and treatment a challenging task. Historically, management decisions have been based on clinico-pathologic features and PSA trends. With an increasing number of aging men in the population at risk for this disease, there are significant implications of these biopsy and subsequent treatment decisions. Risk stratification will help avoid unnecessary biopsies and over-treatment in low risk patients, and guide treatment strategies in high risk patients who will derive the most benefit. Biomarkers are becoming useful adjunctive tools to help risk stratify patients and ultimately guide individual management, either at the decision for initial biopsy or in determining between active surveillance or active treatment with radiation or surgery for localized disease.[4]

Each of the biomarkers presented have unique performance characteristics and are subject to proprietary considerations. Since multiple biomarker tests currently exist with many more in development, it may be difficult for clinicians to decide on which test to use. Large scale prospective studies may help validate biomarker usage

and define clinical applicability but are not being widely adopted. One example of comparative prostate cancer biomarker testing is the recently completed Canary Prostate Active Surveillance Study (PASS).[26] This study examined the association of urinary biomarkers PCA3 and TMPRSS2:ERG (T2:ERG) with biopsy-based reclassification of men on active surveillance. Other factors to consider when deciding to use a specific biomarker are cost and insurance coverage.

The field of precision medicine is rapidly evolving, and our symposium presentation focused on some of the more commonly used FDA approved markers. There are many other biomarkers under study in areas such as liquid biopsies for circulating DNA and the use of genetic testing for prostate cancer risk assessment and management of all stages of disease.[27,28] The future of these precision oncology initiatives will rely on the identification of more patient specific biomarkers. These new markers will exploit the unique inherited and somatic genomic characteristics of the patient and his prostate cancer to further guide diagnosis and treatment in all stages of disease.

** Editors note

In May, 2020 two PARP inhibitors, rucaparib and olaparib, were approved for metastatic castrate resistant prostate cancer with a deleterious BRCA or homologous recombination repair (HRR) gene mutation. □

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