

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Daniel J. George, MD

Prognostic Biomarkers in Early-Stage Prostate Cancer



Eric Klein, MD
Chair, Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

H&O What is the traditional way for oncologists to determine prognosis in early-stage prostate cancer?

EK The tools traditionally used to determine prognosis are the cancer grade based on the Gleason score, the clinical stage based on a digital rectal examination, and the prostate-specific antigen (PSA) level.

H&O What biomarkers beyond PSA are now being used to determine prognosis?

EK There are 4 biopsy-based biomarker tests on the market for men who have not undergone surgery: Oncotype DX prostate cancer test from Genomic Health, Decipher Biopsy from GenomeDx, Prolaris from Myriad Genetics, and ProMark from Metamark Genetics (Table). The way they work is that a biopsy sample is sent to the company laboratory, which analyzes the expression of various genes in the prostate based on RNA and/or protein quantification. The company provides an analysis of the biological aggressiveness of the cancer, which can aid in decision making after biopsy in patients who have early-stage cancer considered to be very low risk, low risk, or intermediate risk per the National Comprehensive Cancer Network (NCCN) guidelines. The Oncotype DX Test has been validated to reflect the biology of the whole prostate, even though the test is based on a small portion of the tumor.

H&O How effective are these biomarker tests for determining prognosis?

EK The results are approximately 10 to 15 percentage points better than those based on just grade, stage, and

PSA level, so they are not perfect but do help significantly. The use of these tests has been validated, and the Centers for Medicare & Medicaid Services covers them in patients whose disease is considered low or very low risk per the NCCN guidelines. Patients with intermediate-risk disease generally need to pay out of pocket if they want to use these tests.

H&O Does ethnicity affect the utility of the biomarker tests?

EK We do not have a lot of data on that issue. In unpublished data from the main study of Oncotype DX, in which approximately 1 in 10 participants were black, the test appeared to perform the same in black and white patients. The utility of the test in other populations, such as Asians and Pacific Islanders, has not been specifically studied.

Table. Molecular Risk Assessment Tests Used in Active Surveillance

Test and Manufacturer	Process Measurements
Decipher Biopsy, GenomeDx	RNA quantification and analysis of gene expression
Oncotype DX, Genomic Health	RNA quantification and analysis of gene expression
Prolaris, Myriad Genetics	RNA quantification and analysis of gene expression
ProMark, Metamark Genetics	Immunohistochemical protein quantification

H&O How are biomarkers being used to determine which patients with early-stage prostate cancer are candidates for active surveillance?

EK A recently published randomized trial and 2 large cohort studies have shown that most men with low-grade cancer do not need any treatment. However, our ability to correctly predict which men fall into that category based on cancer grade is limited. Our predictions also are limited by the standard way of performing prostate biopsy under ultrasound guidance; the extent of a patient's cancer can be missed because the entire prostate is not sampled.

Prognostic markers can tell us the biological potential of a tumor that has been biopsied, and biomarker tests such as Oncotype DX can tell us whether anything worrisome is hiding in the part of the prostate that was not sampled.

Emerging data suggest that 5% to 10% of prostate cancers that are considered low grade on a pathology report actually have molecular features of high-grade cancers. Thanks to molecular markers, we now can learn more about which low-grade cancers on biopsy have the potential to develop into higher-grade cancers. This concept was illustrated by the ProtecT (Prostate Testing for Cancer and Treatment) trial, which was recently published in the *New England Journal of Medicine*. In this trial, 1643 men were randomly assigned to radical prostatectomy, external beam radiation, or active surveillance. The trial found very few deaths at 10 years, which was not surprising, and no difference in the death rates of the 3 groups—although patients in the active surveillance group were more likely to have disease progression or metastasis. However, approximately 10% of patients in the active surveillance group had developed metastatic disease or died of prostate cancer at 10 years, a finding underscoring that the 3 standard features we use—grade, stage, and PSA level—are not perfect predictors of biological potential.

This finding also demonstrates the potential utility of genomic tests to identify men with low-grade cancer on biopsy that may have molecular features of high-grade cancer. Even more importantly, these tests may be able to help us learn which patients undergoing active surveillance will require treatment because they have a tumor that is becoming more aggressive. The ability to identify the best candidates for active surveillance, and then to identify which of these patients need treatment, is going to be the most valuable use of this technology. These biomarker tests will revolutionize the way we use active surveillance to manage patients.

H&O How close are we to using this type of testing in all patients with early-stage prostate cancer?

EK It takes time for new advances to diffuse through the marketplace. Right now, we see areas where many physicians are using these tests and other areas where few physicians are using them. Personally, I like to use them in all my patients who are candidates for active surveillance. Of course, factors such as cost, convenience, and patient

These tests may be able to help us learn which patients undergoing active surveillance will require treatment.

preference all play a role. Most of these tests cost several thousand dollars, although patients generally pay less than that. If a patient is not comfortable with the idea of active surveillance, there is no need to do a test to see whether surveillance is a good choice.

H&O Is the availability of these tests increasing the number of men who are undergoing active surveillance?

EK Yes, it has. When my coinvestigators and I were developing Oncotype DX and validating some of the other biomarker tests, we had 2 motivations. First, we wanted to acquire a better understanding of the biology of prostate cancer. Second, we wanted to change the behavior of physicians and patients by providing them with more information on which to base a decision. Studies have shown that using these tests does increase the number of men for whom urologists recommend active surveillance, and the NCCN guidelines say that physicians should consider using the tests in men with early-stage prostate cancer for this reason.

H&O What other biomarker tests are in development right now?

EK I am not aware of all of them, but some new ones are in development, and companies that already have tests are working on second-generation versions. Some of the

companies whose tests are on the market are going to come out with second-generation tests that measure additional parameters. Furthermore, GenomeDx, the company that manufactures Decipher Biopsy, is expanding its Genomics Resource Information Database (GRID), which is a cloud-based platform for sharing genomic data to allow collaborative research. Gene signatures that predict response to androgen deprivation, radiation, and individual drugs also are in the pipeline.

H&O Can biomarker testing play a role in screening for prostate cancer?

EK That is a potential use for it. As we all know, PSA level is a problematic screening test because it does not distinguish between prostate enlargement and prostate cancer. Some of the next-generation assays, such as the 4Kscore Test from OPKO Health and the Prostate Health Index from Beckman Coulter Diagnostics, can measure multiple isoforms in PSA. There is also a new urine test from Exosome Diagnostics on the market called IntelliScore (or ExoDx Prostate); this test provides information based on 3 genetic biomarkers that can help physicians determine whether a biopsy is warranted. In addition, the University of Michigan's MLabs has a test available called Mi-Prostate Score (MiPS), which combines PSA level with 2 markers for prostate cancer: *T2:ERG* and *PCA3*. With all these tests, diagnostic accuracy is better than with PSA measurement alone.

An ideal screening paradigm would help us find only the cancers that need treatment. We are not there yet, but these tests are a step forward.

Disclosures

Dr Klein has consulted for GenomeDx, Genomic Health, and Metamark Genetics.

Suggested Readings

Bhasin JM, Lee BH, Matkin L, et al. Methylome-wide sequencing detects DNA hypermethylation distinguishing indolent from aggressive prostate cancer. *Cell Rep*. 2015;13(10):2135-2146.

Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):1415-1424.

Knezevic D, Goddard AD, Natraj N, et al. Analytical validation of the Oncotype DX prostate cancer assay - a clinical RT-PCR assay optimized for prostate needle biopsies [published online October 8, 2013]. *BMC Genomics*. 2013;14:690. doi: 10.1186/1471-2164-14-690.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Prostate cancer. v.3.2016. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#prostate. Updated May 26, 2016. Accessed November 21, 2016.

Reichard CA, Stephenson AJ, Klein EA. Molecular markers in urologic oncology: prostate cancer. *Curr Opin Urol*. 2016;26(3):225-230.

Reichard CA, Stephenson AJ, Klein EA. Applying precision medicine to the active surveillance of prostate cancer. *Cancer*. 2015;121(19):3403-3411.

Zhao SG, Evans JR, Kothari V, et al. The landscape of prognostic outlier genes in high-risk prostate cancer. *Clin Cancer Res*. 2016;22(7):1777-1786.