



Caring for Patients With Prostate Cancer Who Are BRCA Positive

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Genomic testing may be a vital component in the medical management of patients with complex clinical phenotypes and cancer.

There are several risk assessment tools and clinical practice guidelines used in the management of localized prostate cancer (PCa). These include the D'Amico classification, the Cancer of the Prostate Risk Assessment (CAPRA) score, the National Comprehensive Cancer Network (NCCN) risk criteria, and the American Urological Association (AUA) clinical practice guidelines.¹⁻⁴ None of these tools incorporate the BRCA1 and BRCA2 genes in the risk assessment or treatment recommendations for localized PCa.⁵ The BRCA mutations are most strongly associated with breast and ovarian cancer risk. However, BRCA mutations also increase susceptibility and disease progression in PCa.⁶ This article illustrates the current knowledge gap in PCa treatment algorithms for the BRCA2-positive patient population.

Traditional risk assessment tools use clinical and pathologic features of PCa, including prostate-specific antigen (PSA) level, Gleason score, tumor stage, and disease burden to measure cancer aggressiveness.^{1,7,8} These criteria are the basis of the AUA and NCCN guidelines for management of clinically localized PCa, which recognize 3 categories of clinically localized disease (low, intermediate, and high risk).^{3,4} The NCCN guidelines (version 1.2016) include a fourth category (very low risk or pathologically insignificant PCa) among some stage

T1c patients, based on additional criteria, including PSA density. Both the AUA and NCCN recommend active surveillance as a treatment option for men with low-risk PCa. The NCCN recently revised its guidelines to state that intermediate-risk patients with PCa with favorable features (Gleason grade 3 and < 50% of positive biopsy cores) may also be considered for active surveillance.³

BRCA MUTATIONS IN PROSTATE CANCER

Estimates of the relative risk of PCa for men with BRCA1 and BRCA2 mutations have varied, but recent data suggest that it is 3.75-fold for BRCA1 mutations and 8.6-fold for BRCA2 by age 65 years.⁹⁻¹¹ Moreover, PCas associated with BRCA1/2 mutations, particularly those in the BRCA2 gene, are often more aggressive and characterized by poor outcomes.^{12,13} The presence of a BRCA2 mutation is a negative prognostic factor in PCa, independent of tumor grade, stage, and PSA levels.¹⁴ Both PCa-specific survival and metastasis-free survival rates following surgical or radiation therapy are significantly lower in the BRCA mutation carriers than in noncarriers.¹⁵ Preliminary results of the IMPACT study demonstrate that targeted PCa screening in men with BRCA1 or BRCA2 mutations may result in identification of tumors more likely to require treatment.¹⁶

As a result of these increased risks, it is recommended that men with BRCA2 mutations begin PCa screening at age 40 years; however, there are no clear guidelines regarding clinical management of PCa in this group of patients.⁵ The lack of guidelines presents a challenge for clinical management of BRCA1/2 mutation carriers with localized PCa who otherwise qualify for active surveil-

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lance. A recent editorial by Bratt and Loman specifically calls for aggressive therapy for patients who are BRCA positive, particularly BRCA2 carriers, suggesting the need to combine early radical local treatment with adjuvant systemic therapy.¹⁷ However, data on the effectiveness of aggressive therapies in patients with PCa who carry BRCA2 mutations are sparse.⁵

GENOMIC TESTS FOR RISK

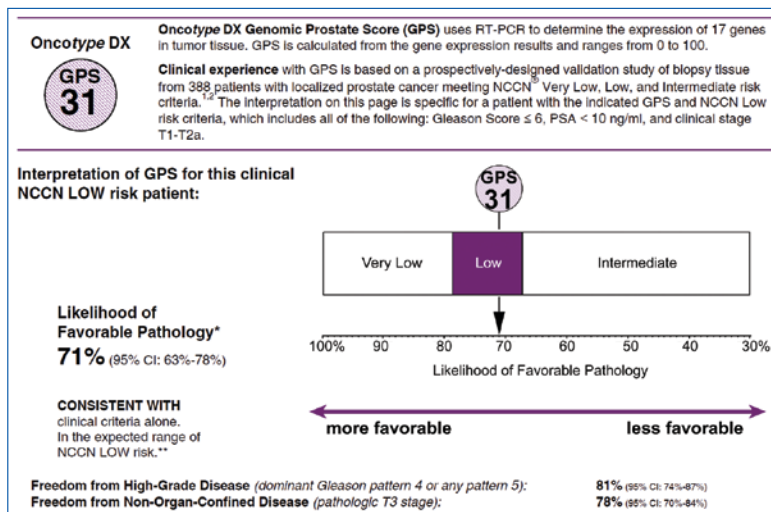
There is growing recognition of the need to include molecular testing to improve risk assessment in PCa. Using traditional risk assessment tools, about 8% of low-risk patients are found to have progressive disease postoperatively.³ Current AUA guidelines from 2007 are silent on the issue of molecular testing.

The 2015 and 2016 NCCN guidelines include molecular testing for better risk stratification of patients with PCa, specifically naming *Oncotype DX Prostate Cancer Assay* (Genomic Health, Redwood City, CA) and *Prolaris* (Myriad Genetics, Salt Lake City, UT).³ However, they do not address molecular BRCA mutation testing.

There are several genomic tests aimed at improving PCa risk assessment. These include *Oncotype DX PCa Assay*; *Prolaris*; *Decipher Prostate Cancer Classifier* (GenomeDx Biosciences, San Diego, CA); and *ProMark* (Metamark Laboratories, Cambridge, MA). These assays are tissue-based and measure gene expression on the RNA or protein level to identify low- or intermediate-risk patients who may be candidates for active surveillance, as well as patients at higher risk who may benefit from closer monitoring or additional therapy after their initial treatment. By 2015, the Centers for Medicare and Medicaid Services had issued positive coverage decisions for several tests.¹⁸

The *Oncotype DX* test is a quantitative real-time polymerase chain reaction assay that measures the expression of 17 genes (12 cancer-related genes and 5 reference genes) representing 4 biologic pathways, including from the androgen signaling, stromal response, cellular organization, and cellular proliferation (Table). *Prolaris* focuses on a larger number of genes in the cell-cycle progression (CCP) pathway (31 cell-cycle-related genes and 15 reference genes). There is no overlap between the 2 gene

Figure 1. Oncotype DX Genomic Prostate Score



sets. Both tests integrate genomic data with clinical and histopathologic characteristics of the tumor to arrive at prognostic information. The *Oncotype DX* test yields a specific Genomic Prostate Score (GPS; scaled 0-100) that is integrated with the patient's NCCN clinical risk group to quantify the likelihood of favorable pathology, which is defined as low-grade organ-confined disease.¹⁹ The *Prolaris* test uses the patient's AUA risk category and then evaluates the patient's risk based on the cell-cycle progression gene panel compared with that risk category. It also provides an estimate of disease-specific mortality as validated by 2 independent cohorts that were managed conservatively initially with watchful waiting.

The authors present a case report of a BRCA2-positive veteran with newly diagnosed low-risk PCa and a history of breast cancer. In addition to evaluating clinical criteria, *Oncotype DX* and *Prolaris* gene expression tests were ordered for this patient. The authors obtained veteran and institutional review board permission. To protect the identity of the patient, minor changes were made to patient demographics.

CASE PRESENTATION

A 68-year-old white man with a history of coronary artery disease, dyslipidemia, and hypertension, was recently diagnosed with PCa. He presented to Genomic Medicine Service to discuss how his BRCA2 mutation

status might impact management decisions for PCa.

Prior to the PCa diagnosis, the veteran had a history of breast and skin cancer. He was diagnosed with invasive ductal carcinoma of the right breast (ER+/PR+/Her2+) at age 62 years and treated with mastectomy and tamoxifen. He had testing at that time, which revealed a BRCA2 mutation: 3773delTT. Squamous cell carcinoma was detected on his right leg and removed at age 64 years. Basal cell carcinoma was removed from his left forehead first at age 65 years, and then residual basal cell carcinoma was removed from the forehead 2 months later.

The veteran was diagnosed with PCa at age 67 years at a non-VA clinic. The urology consult note reported a sudden increase of his PSA level to 5.9. A prostate needle biopsy was performed. The Gleason score was 3 + 3 = 6 in 2 of 12, with < 1% PCa involvement and focal high-grade prostatic intraepithelial neoplasia. The patient was asymptomatic, and his cancer was identified by needle biopsy due to elevated PSA. His clinical stage was T1c. According to AUA and NCCN guidelines, the patient was categorized as low risk, defined as Gleason Score ≤ 6 , PSA < 10 ng/mL, and clinical stage up to T2a.^{3,4} Additionally, the veteran met 3 criteria for the NCCN very low-risk category (stage T1c, < 3 positive biopsy cores and $\leq 50\%$ cancer in any core). However, because he was initially diagnosed at a non-VA clinic, his PSA density (the remaining criterion) was not available to the VA urologist. Therefore, the low-risk category was assumed for molecular test interpretation.

The non-VA urologist recommended active surveillance. The VA urologist agreed that active surveillance was an appropriate treatment recommendation at this time. However, the veteran and his family members remained concerned that his PCa might be more aggressive due to his BRCA2 mutation, and they worried that active surveillance would result in a worse outcome. Their concern was exacerbated by the veteran's comorbidities, which could have potential implications on the timing of surgical options. The patient expressed these concerns to his VA primary care physician, who then referred him to the VA Genomic Medicine Services.

Genetic Consult

The genetic counselor scheduled a telegenetics consult and conducted an assessment of the veteran, which included a review of his medical history, mutation status, and relevant family history. The family history was consistent with hereditary breast/ovarian cancer.

However, the primary reason the veteran underwent genetic testing was the diagnosis of breast cancer in a male. The genetic counselor provided the patient with information relevant to his mutation carrier status, including that men with BRCA2 mutations are at increased risk of developing more aggressive PCa, have higher rates of lymph node involvement, and greater mortality compared with men without BRCA2 mutations. The veteran was informed that there were no published guidelines that suggest PCas in BRCA2 carriers should be treated differently from sporadic PCas.

Tumor Testing Strategy

Although the veteran was comfortable with active surveillance at the time of consultation, he was concerned that, given his comorbidities, it would be better to pursue surgery sooner. The veteran asked the genetic counselor for more information about his prognosis given his BRCA2 status. The genetic counselor discussed possible use of tumor gene expression profiling and informed him about 2 active studies within the VA that are evaluating the clinical utility of gene expression tests for PCa risk stratification (Oncotype DX at Genomic Health and Prolaris at Myriad Genetic Laboratories). The veteran expressed an interest in having his biopsy tissue tested by both assays. Tumor biopsy tissue was obtained and sent to both Genomic Health and Myriad Genetics for testing. Neither test incorporated the veteran's other health conditions or his BRCA mutation status into risk stratification results or the patient report.

Test Results

The Oncotype DX GPS result for this NCCN low-risk patient was 31 (Figure 1). This score corresponds to a likelihood of favorable pathology at radical prostatectomy of 71% (95% confidence interval [CI]: 63%-78%). Favorable pathology is defined as freedom from high-grade (Gleason score > 4+3) and/or nonorgan-confined (pT3) disease. This GPS result was consistent with the range of risk expected for NCCN low-risk patients based on the validation cohorts for the assay. The estimate of likelihood of favorable pathology would be modified if the PSA density result were available and if it placed the patient in the NCCN very low-risk category.

The Prolaris report demonstrated a score of 0.4 (Figure 2). This puts the veteran in the 94th percentile of contemporary U.S. men who are AUA low risk. The CCP score makes his cancer more aggressive than most AUA

low-risk men, and the projected 10-year disease-specific mortality is 3%. In conjunction with the patient's BRCA2 status, he may benefit from definitive intervention. If active surveillance is chosen, careful and regular follow-up for disease progression is mandated.

Interpretation of Genomic Testing in PCa

For both tests, the results are derived from 2-tiered calculations. For *Oncotype DX*, the gene expression measurement yields the GPS, which is then integrated with the patient's clinical and pathologic information to yield the likelihood of favorable pathology. Although the *Oncotype DX* GPS is an independent measure of disease aggressiveness, on the patient report, the GPS is combined with the NCCN clinical risk group to provide a likelihood of favorable pathology. Therefore, 2 patients with the same GPS but different levels of clinical risk will have different likelihoods of favorable pathology.

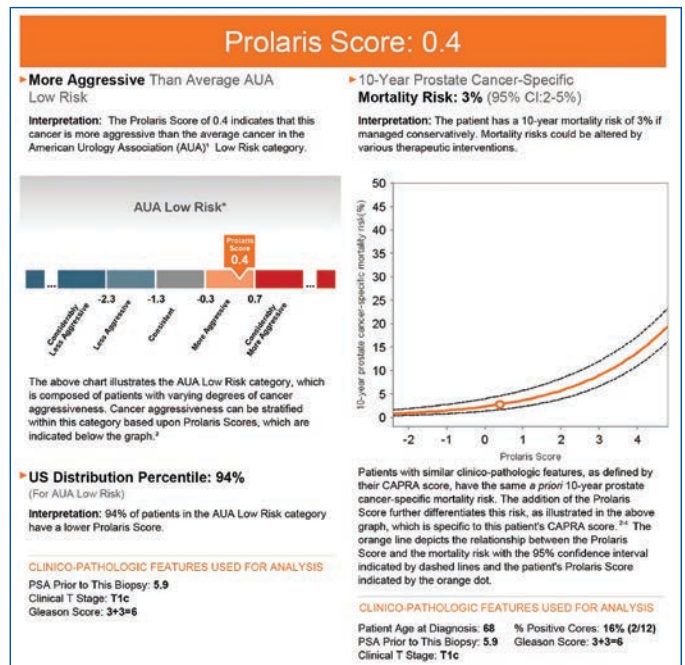
The Prolaris test provides the Prolaris CCP score as well as the percentile group of patients with a lower score within the same risk category. Also, the Prolaris test yields a numerical 10-year PCa-specific mortality risk. The Prolaris score has been shown to impact therapeutic decisions in patients with newly diagnosed PCa.²⁰

Recently, Myriad defined a threshold for active surveillance combining the CCP and CAPRA scores.²¹ Myriad validated this cutoff in 2 cohorts of men initially managed conservatively. Although the model predicts up to 3.2% disease-specific mortality, there were no observed deaths during a decade of follow-up. Myriad reports that by using this cutoff in contemporary patients tested commercially with Prolaris, a health care system could increase the percentage of men who would fit current criteria for active surveillance from 36% to 60% with no increase in risk of disease-specific mortality.

The results of these 2 tests are presented in 2 different formats and provide risk estimates for different clinical endpoints, making it challenging for a clinician to directly compare them. Moreover, each genomic test is based on a different set of genes and uses different clinical risk criteria (AUA vs NCCN), which may result in different test output. Finally, and most relevant to the case described here, there is no evidence-based consensus on how to interpret these test results in the context of a BRCA2 mutation.

Based on the published literature reporting that

Figure 2. Prolaris Cell Cycle Progression Score



BRCA2 mutations are associated with more aggressive disease, one prediction would be that test scores from genomic assays such as *Oncotype DX* and Prolaris would tend to be higher in BRCA2 carriers than those of the overall population of PCa patients. This has, in fact, been reported for the *Oncotype DX* Breast Cancer Assay recurrence score in women who are BRCA carriers.²² Further research is required to ascertain whether this will be true for *Oncotype DX* GPS and Prolaris CCP score in PCa. The mechanism of action that predisposes BRCA2 mutation carriers to development of the more aggressive variant of PCa may not be detectable by the genomic markers included in the *Oncotype DX* PCa and Prolaris tests. The degree to which a mutated BRCA2 gene may interact with the genes comprising these assays and the reported tumor aggressiveness is not yet understood but deserving of future study.

Treatment Recommendation and Patient's Decision

After considering his test results, the veteran chose active surveillance. The sum of clinical, pathologic, and molecular factors, combined with the patient's preference, determined his course of treatment. Because prostatectomy was not performed, it has not been positively determined whether or not the patient harbors aggressive disease. As the molecular test results place

Table. Comparison of Oncotype DX Prostate Cancer Assay and Prolaris test

Test name	Oncotype DX Prostate Cancer Assay	Prolaris
Laboratory	Genomic Health, Inc.	Myriad Genetic Laboratories, Inc.
Indication	Positive prostate biopsy	Positive prostate biopsy or radical prostatectomy
Test timing	At initial diagnosis (pretreatment specimen)	At initial diagnosis (pretreatment specimen) or post-surgery
Genes	12 cancer-related genes: androgen signaling (<i>AZGP1</i> , <i>KLK2</i> , <i>SRD5A2</i> , <i>FAM13C</i>); cellular organization (<i>FLNC</i> , <i>GSN</i> , <i>TPM2</i> , <i>GSTM2</i>); cell proliferation (<i>TPX2</i>); stromal response (<i>BGN</i> , <i>COL1A1</i> , <i>SFRP4</i>) + 5 reference genes	31 cell cycle progression genes: <i>FOXM1</i> , <i>CDC20</i> , <i>CDKN3</i> , <i>CDC2</i> , <i>KIF11</i> , <i>KIAA0101</i> , <i>NUSAP1</i> , <i>CENPF</i> , <i>ASPM</i> , <i>BUB1B</i> , <i>RRM2</i> , <i>DLGAP5</i> , <i>BIRC5</i> , <i>KIF20A</i> , <i>PLK1</i> , <i>TOP2A</i> , <i>TK1</i> , <i>PBK</i> , <i>ASF1B</i> , <i>C18orf24</i> , <i>RAD54L</i> , <i>PTTG1</i> , <i>CDCA3</i> , <i>MCM10</i> , <i>PRC1</i> , <i>DTL</i> , <i>CEP55</i> , <i>RAD51</i> , <i>CENPM</i> , <i>CDCA8</i> , and <i>ORC6L</i> + 15 reference genes
Biological material	FFPE tissue from prostate needle biopsy	FFPE tissue from prostate needle biopsy or prostatectomy specimen
Measurement	Gene expression (RNA)	Gene expression (RNA)
Outcome	GPS (0 to 100; a higher score predicts more aggressive disease)	Prolaris Cell Cycle Progression Score (-3 to 7; each 1-unit increase doubles the risk)
Predictions	1. Differentiates risk within different NCCN clinical categories. 2. Predicts likelihood of favorable pathology, based on GPS result combined with the patient's clinical risk group	1. Differentiates patients within similar AUA risk category (estimated based on clinical characteristics) 2. Estimates a 10-year PCa-specific mortality risk

Abbreviations: AUA, American Urological Association; FFPE, formalin-fixed paraffin-embedded; GPS, Genomic Prostate Score; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer.

the patient at the high end of the low-risk group, the VA urologist recommended close monitoring and suggested a follow-up biopsy with magnetic resonance-ultrasound fusion guidance.

CONCLUSIONS

Molecular testing found that the patient's PCa stage and grade are consistent with NCCN low risk (Oncotype DX) and that the disease-specific mortality risk is slightly higher than predicted by clinical features alone (Prolaris). Previous studies have shown that molecular testing in men with PCa provides information that influences clinical decisions. The findings reported here suggest that molecular testing may also be a vital component in the medical management of patients with complex clinical phenotypes and common chronic conditions. Additional studies are necessary to evaluate whether the finding

reported here is typical of individuals diagnosed with PCa who also have a BRCA2 mutation.

For any new genomic test to be clinically useful, its results must have clinical actionability. In this case, the clinical decision point was whether to recommend immediate definitive treatment or active surveillance. For this patient, the Oncotype DX assay provided a likelihood of favorable surgical pathology of 71% (or conversely a 29% risk of unfavorable pathology); by comparison, the Prolaris CCP score provided a 3% estimate of PCa-specific mortality at 10 years. A key question is: How do clinicians perceive the actionability of risk estimates for these different endpoints?

The current case illustrates the challenges that rapidly developing genomic medicine pose for physicians trying to optimize care and communicate results to patients in a meaningful and consistent manner. For example,

some urologists find the different 2-tiered calculations confusing. When laboratories use proprietary scales based on internally developed algorithms, differing interpretations are to be expected. The risk-assessment tests described here use different algorithms, and their interpretations are based on clinical categories from different sets of guidelines. This underscores the need for better standardization of PCa care.²³

Oncology and urology professional associations should collaborate to develop consistent guidelines for use of new technologies in the management of PCa. A positive example is the evolution of testing recommendations in lung cancer, which initially varied between professional entities. In April 2013, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology jointly issued a unified clinical practice guideline on molecular testing in patients with lung cancer.²⁴ In October 2014, the American Society of Clinical Oncology issued an endorsement of the CAP/IASLC/AMP guideline.²⁵ As the number of complex tests being used in PCa increases, it will be important for professional associations such as AUA and NCCN to collaborate in evaluating utility of innovations to make consistent recommendations.

Author disclosures

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