Genetics and Screening in Prostate Cancer

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KEYWORDS

• Prostate cancer • Germline genetic testing • Somatic mutations
• Polygenic risk scores • Health disparities • Precision oncology

KEY POINTS

- Prostate cancer is one of the most heritable malignancies, with germline mutations in DNA repair pathways significantly influencing disease risk, aggressiveness, and age at onset.
- Germline and somatic genetic testing play a critical role in identifying patients who may benefit from targeted therapies, including poly (ADP-ribose) polymerase inhibitors and immune checkpoint inhibitors.
- Current guidelines recommend genetic testing based on disease stage, histology, ancestry, and family history, though growing evidence supports broader or universal testing approaches.
- Emerging technologies such as Polygenic Risk Scores, genomic classifiers, digital histopathology, and circulating tumor DNA offer new opportunities to refine risk stratification and personalize care.

INTRODUCTION

In 2022, an estimated 3 million men were living with prostate cancer in the United States. Notably, localized prostate cancer has a relatively good prognosis with an overall 5 year relative survival rate of 97.9%. However, this 5 year relative survival sharply declines to 37.9% in those with distant metastasis.[1] The discrepancy in survival between localized and metastatic disease highlights the need for evidence based screening guidelines that include recommendations on genetic testing to minimize the number of people diagnosed with advanced disease, thus limiting prostate cancer related deaths.

Prostate cancer's high prevalence results in a large mortality burden on the US health care system. The predicted number of deaths from prostate cancer in 2025

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Abbreviations	
ADT	androgen deprivation therapy
AI	artificial intelligence
ARPIs	androgen receptor pathway inhibitors
ctDNA	circulating tumor DNA
GCs	genomic classifiers
GGT	germline genetic testing
MMAI	multimodal artificial intelligence
NCCN	National Comprehensive Cancer Network
PARPi	poly (ADP-ribose) polymerase inhibitors
PGI	Polygenic Index
PRS	Polygenic Risk Score
RNA	ribonucleic acid
SNPs	single nucleotide polymorphisms

is over 35,000 men, making it the second highest cause of cancer related deaths behind cancer of the lung and bronchus. However, non-Hispanic Black men carry a disproportionate burden of prostate cancer related deaths with an incidence of 36.9 cases per 100,000 persons compared with their non-Hispanic White counterparts with an incidence of 18.4 cases per 100,000 persons.[1] This increased burden in minority populations is also reflected in the fact that non-Hispanic Black men and Hispanic men are being diagnosed with increasingly higher rates of advanced disease. An 18-year analysis of over 300,000 prostate cancer cases showed that distant stage disease is being diagnosed at increasing rates, with Hispanic and non-Hispanic black males experiencing the largest rise at 8.0% and 7.4% per year, respectively.[2]

Independent of race, prostate cancer has shown to be one of the most heritable types of cancers. One study of over 26,000 patients from the Swedish-Family Cancer Database found that if a patient's father had prostate cancer, he had a 2.1 times greater risk of developing the disease. Notably, this risk increased to 17.7 if the patient had 3 brothers diagnosed with prostate cancer.[3] Expanding upon this, the Nordic Twin Studies used a cohort of over 4000 prostate cancer cases to calculate heritability. They estimated it to be 57%, which is higher than colon, breast, and ovarian cancer. Analyses of the same cohort found a decreased time between diagnosis of prostate cancer in monozygotic twins (3.7 years) compared with dizygotic twins (6.1 years), further supporting the role that genetics plays in prostate cancer.[4–6]

It is important to distinguish between heritable prostate cancer and simply having a familial predisposition to it. Prostate cancer that is inherited aligns with the Hopkins Criteria in which one of the following is true: (1) prostate cancer in 3 or more first degree relatives, (2) prostate cancer in 3 consecutive generations, or (3) 2 family members diagnosed prior to 55 years of age.[7] In addition to this criteria, hereditary prostate cancer is often seen in patients with a family history of hereditary breast/ovarian cancer and Lynch syndrome,[8] which are associated with specific genetic mutations. As such, genetic testing plays a particularly important role for those with this type of family history.

Prostate cancer's disproportionate impact on minority populations and strong hereditary association makes genetic testing an important consideration when screening patients. The question is not if genetic testing is important, but who should be tested, when they should be tested, and how it should guide patient care. This article reviews both germline and somatic mutations, who should be genetically screened, what tests are currently being used, and future considerations for genetic testing in prostate cancer.

GERMLINE GENETIC MUTATIONS

Germline Mutations and Their Clinical Relevance

In heritable prostate cancer, the germline genetic mutations passed from parent to offspring have been observed to negatively impact the DNA repair process through 2 key mechanisms: Homologous Recombination and Mismatch Repair. Generally, Homologous Recombination is a cell's ability to repair double stranded breaks within its DNA and Mismatch Repair is a cell's ability to repair insertions, deletions, and mismatched base pairs within the strand of DNA.[8] Mutations in these pathways have been associated with an increased risk for prostate cancer, a more aggressive disease course, and an earlier onset of the disease.

The germline mutations that impact the homologous recombination repair process are BRCA1, BRCA2, ATM, CHEK2, PALB2, and HOXB13.[9] While both pathogenic variants of BRCA1/2 mutations increase a person's risk of prostate cancer, BRCA2 mutations confer a markedly increased risk compared with BRCA1. The relative risk of developing prostate cancer associated with a BRCA2 mutation ranges from 4.7 to 8.6, while the relative risk associated with a BRCA1 mutation is roughly 3.8.[10–12] Notably, the risk of being diagnosed with prostate cancer prior to 65 years of age is significantly higher in those with a BRCA2 mutation. On average, those with a BRCA2 mutation are diagnosed 3 years earlier than noncarriers.[13] Importantly, BRCA1/2 carriers are associated with more aggressive forms of prostate cancer. Compared with non-carriers, those with BRCA1/2 mutations are more frequently associated with Gleason greater than or equal to 8, T3/T4 stage, nodal involvement, and metastases at diagnosis.[14]

Of the germline mutations associated with prostate cancer, pathogenic BRCA1/2 variants are the most common and confer the greatest risk. However, ATM, PALB2, HOXB13, and CHEK2 also play significant roles. Loss of the ATM gene has shown to increase the risk of developing prostate cancer (OR 4.4) and predisposes an individual to being diagnosed with prostate cancer at an earlier age.[15] While PALB2 mutations confer only a modest risk for developing prostate cancer, their presence significantly increases the risk of developing Gleason 8 to 10 disease (OR 8.05).[16] HOXB13 mutations predispose a patient to developing prostate cancer but are not associated with higher grades of disease.[17] Lastly, CHEK2 mutations increase the likelihood of developing prostate cancer, but only specific mutations (eg, c.1100delC) have shown to be associated with poor patient outcomes.[18]

Aside from the risks that these germline mutations confer, their presence also has therapeutic and diagnostic implications. Therapeutically, the presence of BRCA1/2 often qualifies patients with metastatic castration-resistant prostate cancer (mCRPC) for treatment with poly (ADP-ribose) polymerase inhibitors (PARPi). The PROfound trial showed an improved overall survival in these patients treated with Olaparib, resulting in the American Society of Clinical Oncology recommending PARPis to patients who had previously been on androgen receptor pathway inhibitors (ARPIs).[19] From a diagnostic standpoint, PSA has been shown to be more predictive of prostate cancer in carriers of BRCA1/2 compared with non-carriers (OR 1.27).[20] Similarly, PARPis have shown efficacy in mCRPC patients with PALB2 mutations. An FDA pooled analysis demonstrated a clinically, but not statistically significant benefit for mCRPC patients with a PALB2 mutation receiving PARPis in terms of radiographic progression-free survival (HR 0.52) and overall survival (HR 0.78).[21] Notably, this effect of PARPis is not seen in those with ATM or CHEK2 mutations.[22]

Compared with homologous recombination, germline mutations in the mismatch repair pathway are relatively rare. One study of 1016 men with prostate cancer found

only 7 had an MMR deficiency.[23] Despite this, these mutations confer a significant risk for developing prostate cancer and are associated with a more clinically and pathologically aggressive disease. Specifically, germline mutations in this pathway have shown to be associated with higher Gleason scores, intraductal histology, and an increased risk for metastatic disease.[24]

An important consideration in cases of MMR deficient prostate cancer is Lynch Syndrome, which is due to a mutation in 4 of the genes that control the mismatch repair process: MLH1, MSH2, MSH6, and PMS2.[25] Notably, this syndrome has shown to double a person's risk of developing prostate cancer,[26] but is only seen in 0.6% of advanced prostate cancer cases.[27] Because of the associated risk, the National Comprehensive Cancer Network (NCCN) recommends a referral to genetic counseling to assess for Lynch Syndrome if an MMR deficiency is found on tumor analysis.[28]

Notably, clinical trials have shown a good response to PD-1 inhibitors in MMR deficient patients with advanced prostate cancer. One study of 27 men with MMR deficient metastatic prostate cancer showed that 53% of the patients had a greater than or equal to 50% reduction in their PSA and that 64% had clinical/radiographic progression free survival at 6 months in response to a PD-1 Inhibitor.[29] Another study showed that the time to this greater than or equal to 50% reduction in PSA in response to Pembrolizumab was 12 weeks.[24] The therapeutic benefits of PD-1 inhibitors seen in the KEYNOTE trials resulted in the FDA giving full approval for the use of Pembrolizumab in cases of solid tumors with MMR deficiency and microsatellite instability, such as those with metastatic prostate cancer.[30–32]

Who Should Undergo Germline Genetic Testing

Per the 2026 NCCN guidelines (**Box 1**), genetic testing is indicated based on multiple factors. Most notably, it is recommended in cases of advanced prostate cancer, certain types of histology, and relevant personal/family history. If the criteria are met, the guidelines recommend testing for specific genes that have historically been associated with a more aggressive disease course.

Regarding disease specific criteria, genetic testing is currently indicated if a patient is diagnosed with Stage IVB, Stage IVA, or High/Very High-Risk prostate cancer. Stage IVA is prostate cancer that has shown regional lymph node involvement,

Box 1
Prostate cancer genetic testing recommendations

Localized prostate cancer
1. Germline testing (primary targets: BRCA2, ATM, CHEK2, HOXB13, MMR)–Strongly consider if:
   a. High risk/very high risk
   b. Strong family history
   c. Ashkenazi Jewish ancestry
2. Tissue Genomic Biomarkers (Decipher, Prolaris, GPS Oncotype Dx)
   a. Not routine for all patients
   b. Use selectively if results alter Shared Decision-Making (SDM).

Advanced prostate cancer
1. Germline Testing:
   a. Strongly recommended for all metastatic patients regardless of family history
   b. Primary targets include BRCA1/2, ATM, CHEK2, PALB2, MMR genes
2. Somatic (Tumor) Testing:
   a. Mandated to guide targeted therapy
   b. Identify eligibility for PARP inhibitors (BRCA/HRR) and immunotherapy (MSI-H/dMMR)

particularly in the pelvis. Stage IVB is prostate cancer that has shown distant metastasis, namely to the bones, liver, and lung. High Risk prostate cancer are those patients with clinical T3-T4 disease, Grade Group 4 or 5, and a PSA greater than 20 ng/mL. Very High Risk prostate cancer has the same criteria as High Risk with the caveat that the patient has a PSA greater than 40 ng/mL.[33]

Genetic testing can also be considered in patients with certain types of histology seen on biopsy. The 2 most notable types are cribriform and intraductal. These histologic variants have shown to be associated with higher rates of Gleason 4 and 5 tumors.[34] They have also been shown to more commonly contain mutations in the mismatch repair process, specifically in the MSH2 and MSH6 genes.[35] As mentioned earlier, mutations in these specific genes are also highly prevalent in Lynch Syndrome, making genetic testing in these patients more prudent.

The NCCN guidelines also recommend genetic testing in patients with a specific ancestry, family history, or diagnosis of prostate cancer less than or equal to 55 years of age. Notably, the guidelines indicate testing patients of Ashkenazi Jewish descent. Despite this population having similar rates of prostate cancer to those of European ancestry, they are more likely to harbor BRCA2 mutations.[36,37] Regarding family history, genetic testing is indicated if a patient has greater than or equal to 1 close blood relative with any of the following: breast cancer at age less than or equal to 50 years of age, male breast cancer, ovarian cancer, pancreatic cancer, or metastatic, node positive, or Very High/High risk prostate cancer. Additionally, patients should undergo genetic testing if they have greater than or equal to 3 close blood relatives with any grade of prostate cancer and/or breast cancer on the same side of the family.[33]

While guidelines currently do not address universal germline genetic testing (GGT) in patients with prostate cancer, there is growing evidence supporting the practice of universal GGT. One multisite study showed that of patients with prostate cancer and a germline pathogenic variant, roughly 30% did not meet criteria for genetic testing according to their primary cancer and 45% did not meet criteria for genetic testing according to their family history.[38] Similarly, the PROCLAIM trial found no significant difference when comparing the prevalence of pathogenic variants in patients that met criteria for genetic testing and those that did not meet criteria.[39] Notably, this disparity is further exaggerated in non-White populations where it has been shown that only 7% of GGT is performed in Black patients compared with 73% of White patients.[40] Studies that advocate for universal GGT note that it would provide potentially useful therapeutic information for patients, improve equity and access to GGT, and prevent missing patients with actionable germline mutations.[41]

Genetic Tests for Germline Mutations

Traditional genetic testing looks for the monogenic, high penetrant variants (eg, BRCA1/2, ATM, CHEK2, PALB2, and HOXB14) that have shown to be associated with an increased risk for prostate cancer. However, more studies are discovering smaller single nucleotide polymorphisms (SNPs) that influence an individual's risk for developing this disease. To date, there are over 200 known genetic variants associated with prostate cancer.[42] Individually, these SNPs do not drastically impact a person's risk. However, their effects are amplified when combined. A developing clinical tool that looks at the cumulative effects of individual genetic variants is a Polygenic Index (PGI) or Polygenic Risk Score (PRS).

Genome wide association studies have identified individual genetic variants and determined their effect size on developing prostate cancer. PGIs and PRSs calculate a patient's personal risk by adding the effect size of each genetic variant a person

harbors. Currently, there are over 80 PRSs with the smallest including 4 SNPs and the largest including over 6 million.[43] Collectively, these risk assessment tools have shown modest results. A meta-analysis of 16 studies combined various PRS and found an AUC of 0.63 in regards to identifying prostate cancer in White men, which was similar in accuracy to PSA and family history. Notably, this study found that when you combined a PRS with other clinical variables the AUC rose to 0.74, indicating greater accuracy in identifying significant disease.[44]

Of the existing PRSs, there are 5 particularly reputable models that have each been validated in large, multi-ethnic populations: PRS269, PHS290, PHS2, CanRisk-Prostate, and FinRSPC. The developers of PRS269 compared 107,247 prostate cancer cases to 127,006 controls to develop a risk stratification model that incorporated 269 SNPs. The authors found that patients in the top decile of risk for developing prostate cancer had an odds ratio of 5.06, 3.74, 4.47, and 4.15 in patients of European, African, East Asian, and Hispanic descent, respectively.[42] PHS290 is a tool that was developed by looking at 590,750 veterans from the Million Veteran Program to predict the risk of developing lethal prostate cancer. When comparing those in the top 20% of risk to those in the bottom 20%, the hazard ratio for developing lethal prostate cancer was 4.42.[45] PHS2 includes 46 SNPs in its model and not only looked at risk of prostate cancer, but stratified cases by looking at risk for aggressive forms of the disease (Gleason $\geq$ 7, PSA $\geq$ 10, T3-T4 staging, metastasis). When comparing the top quintile to the bottom quintile, they found a hazard ratio of 5.88 for developing an aggressive form of prostate cancer.[46] The CanRisk-Prostate model uniquely incorporates known pathogenic variants (BRCA1/2 and HOXB13), low-risk SNPs, and personal family history of cancer into their risk calculator. Using this calculator, 86.3% of the prostate cancers developed within 10 years were within men that were in the top 50% of risk.[47] FinRSPC looked at a Finnish Population of 2783 prostate cancer patients and 2400 controls to develop a model that includes 55 SNPs in the analysis. In addition to looking at prostate cancer risk, this model uniquely found that 8.3% of patients in the bottom quartile had PSA values greater than or equal to 4 compared with 18.7% in the top quartile.[48]

PRSs have shown benefit in stratifying risk for developing prostate cancer, guiding therapeutic and diagnostic interventions, and identifying novel prostate cancer markers. While many of these PRS models have been validated and have shown clinical significance, guidelines currently do not contain recommendations pertaining to their use. Despite this, evidence has pointed to using these tools in conjunction with a patient's histologic features, personal medical history, and family cancer history to guide management more comprehensively. As these tools improve and more SNPs are revealed in genome wide association studies, the implications and impact of their daily use will become more evident.

SOMATIC MUTATIONS

Somatic Mutations and Their Clinical Relevance

Somatic mutations are genetic alterations that exist within tumor cells. Unlike germline mutations, these are not inherited but change over time due to genetic instability and/or selective pressure from therapy. Testing for somatic mutations is performed to guide therapy because specific mutations are susceptible to different treatment modalities.[49]

The 2026 NCCN guidelines recommend tumor molecular and biomarker analysis for patients with metastatic disease. They recommend testing for BRCA1/2, ATM, PALP2, FANCA, RAD51D, CHEK2, and CDK12. The guidelines also specify testing for genes

associated with MSI-H and Mismatch Repair in patients with mCRPC. It is also strongly recommended to biopsy metastatic lesions, which may include a lymph node biopsy. If a metastatic biopsy cannot be performed, the recommendation is to test for somatic mutations using plasma circulating tumor DNA (ctDNA) during biochemical and/or radiographic progression. The guidelines also specify that re-evaluation may be needed at the time of cancer progression because the molecular profile of the tumor may change as a result of treatment.[28]

The most common somatic mutations seen in prostate cancer are ETS family gene fusions, alterations to the androgen receptor (AR) pathway, TP53, PTEN, and DNA damage repair genes (HRR and MMR).[27] ETS family gene fusions are the most common somatic mutation in prostate cancer and are known early drivers of disease progression.[50] While the prognostic implications of ETS family gene fusions are up for debate, they may be more responsive to androgen deprivation therapy (ADT) because they often fuse with TMPRSS2, an androgen receptor gene.[51] Mutations to the AR pathway are seen in up to 84% of mCRPC and confer a poor prognosis because these tumors are resistant to ADT and AR Pathway Inhibitors (eg, Enzalutamide, Apalutamide, Darolutamide, and Abiraterone).[52] TP53 mutations are seen in 36% of patients with metastatic prostate cancer, confer a 76% increased risk of death and 62% increased risk of disease progression, and are associated with persistence after radical prostatectomy.[27,53,54] Notably, TP53 mutations often result in resistance to standard therapies, necessitating enrollment in clinical trials or the use of novel therapies.[55] PTEN deficiencies are seen in up to 50% of mCRPC cases due to mutations in the P13K-AKT–mTOR pathway conferring resistance to ADT.[56] As such, patients with a PTEN mutation have a more aggressive disease course and worse prognosis, with one study showing a 61% increased risk of death.[57] Similar to germline mutations, genetic aberrations in the homologous recombination and mismatch repair pathways are associated with higher Gleason grades and risk for metastasis.[19] Somatic mutations in the homologous recombination and mismatch repair pathways have also shown susceptibility to PARP-1 inhibitors and PD-1 inhibitors, respectively.[30–32]

Seeing that somatic mutations are harbored by the tumor itself, testing for these mutations is centered on tissue sampling. The 3 types of testing that will be addressed in this section are tumor-derived genomic classifiers (GCs), digital histopathology-based tests, and plasma ctDNA. GCs offer prognostic and therapeutic information by analyzing the ribonucleic acid (RNA) expression profile of tumors. Digital histopathology-based tests are digitally uploaded pathology slides that use artificial intelligence (AI)-based technology to analyze for predictive biomarkers. Lastly, plasma ctDNA provides a noninvasive method of detecting actionable somatic mutations.

TUMOR-DERIVED GENOMIC CLASSIFIERS

Several prostate cancer tissue-based molecular assays have been developed to improve risk stratification and aid in clinical decision making. In general, these tools are only recommended when they have the potential to change management, and only those with high-quality, long-term clinical trial data with prospective validation should be utilized.[28] Tests range in price from $3900 to $5150.[58] Examples of patients for whom tissue-based genomic markers may help clarify risk include patients with high-volume, low-risk, or favorable intermediate-risk prostate cancer who are interested in active surveillance or men with high-risk features for treatment intensification.

Pathologists should primarily select areas of highest cellularity and specific adverse pathology growth patterns for molecular testing. For RNA-based tests, a single 1 mm

core punched from the tumor is generally sufficient to obtain a test outcome, but more tissue is needed for DNA-based tests.[58]

Decipher 22 Gene Classifier

Decipher is the most extensively validated tissue-based genomic assay, analyzing 22 genes from prostate biopsy and prostatectomy specimens to predict metastatic risk and guide treatment decision. The Decipher risk score ranges from 0 to 1, with higher scores indicating more aggressive tumor biology. The assay has level 1 evidence from multiple post-hoc analyses of randomized phase III trials across different risk groups and clinical scenarios.[59]

For patients with localized intermediate-risk, high-risk, or very high-risk prostate cancer, Decipher has been shown to help inform decisions on duration of ADT. Patients with high Decipher scores (>0.6) and NCCN high- or very high-risk disease derive a greater absolute benefit from long-term ADT compared with those with low Decipher scores (<0.45). Similarly, among patients with intermediate-risk disease treated with radiation therapy alone, those with high Decipher scores have a significantly higher risk of distant metastasis at 10 years compared with those with low scores (16% vs 4%, respectively), suggesting that Decipher testing can help identify which intermediate-risk patients are most likely to benefit from the addition of ADT.[60]

In the post-biopsy and post-prostatectomy settings, Decipher independently predicts distant metastasis, prostate cancer-specific mortality, and overall survival. Among patients undergoing adjuvant radiation after prostatectomy, those with high Decipher scores demonstrate a greater benefit from the addition of systemic ADT compared with those with low scores.

Future directions lay in multiple ongoing biomarker-directed randomized trials (eg, NGR GU-009 [PREDICT-RT], GU-010), which will provide prospective evidence on whether Decipher-guided treatment intensification improves oncologic outcomes.[28]

Genomic Prostate Score

The Genomic Prostate Score (GPS), previously known as Oncotype Dx, is a 17-gene expression assay that combines mRNA gene expression results with clinical risk factors to predict the likelihood of Grade Group 3 or greater disease or extracapsular extension at radical prostatectomy. The test generates a score ranging from 0 to 100 that stratifies patients into risk categories for adverse pathology. The evidence base for GPS is primarily from retrospective studies, with more limited prospective validation compared with Decipher.[58]

In the Canary PASS active surveillance cohort (432 patients), adding GPS to clinical variables (PSA density and diagnostic grade group) did not significantly improve adverse pathology stratification (HR 1.17, 95% CI 1.00–1.43, P = .066), and there was no association with subsequent biopsy upgrade.[28] Importantly, a randomized trial raised concerns about GPS use in active surveillance candidates. Among 200 patients with NCCN very low to favorable-intermediate risk disease, GPS testing decreased the relative odds of choosing active surveillance by approximately 50%, with patients with lower health literacy being 7 fold less likely to choose active surveillance after receiving GPS results.[61]

Prolaris

Prolaris tissue-based assay uses biopsy and prostatectomy tissue to evaluate disease aggressiveness based on the expression of 31 genes (originally 46 genes) involved in cell cycle progression. Results predict the likelihood of clinical progression after treatment and prostate cancer mortality within 10 years with watchful waiting. Similarly to

GPS, the evidence for Prolaris lacks prospective data and consists primarily of retrospective institutional and tumor registry studies.[58]

For intermediate-risk prostate cancer, Prolaris has demonstrated value in appropriately identifying active surveillance candidates. A retrospective study of 3204 NCCN intermediate-risk patients showed that those recommended to active surveillance by Prolaris had a very low risk of metastasis (0.37% [95% CI 0.09%–1.47%]) within 5 years. Another study of 3208 patients found that active surveillance selection was approximately 2 times higher in patients recommended to AS by Prolaris, with 1.5 times higher 3 year AS durability.

Multiple studies have documented Prolaris's influence on clinical management. In a prospective registry study of 305 patients, 65% of cases showed a change in treatment recommendations after receiving Prolaris results, with a 37.2% reduction in interventional therapy recommendations and a 49.5% reduction in surgical interventions.[62]

Digital Histopathology-based Tests (ArteraAI)

The advent of AI has allowed for improved clinical tools that can factor in multiple variables to provide more comprehensive diagnostic, prognostic, and predictive information. In prostate cancer, a developing technology are tests centered on digital histopathology. Digital histopathology-based tests use AI-based algorithms, most often neural networks, to analyze digitally uploaded biopsy slides. These tests then factor in patient demographics, clinical staging, and biochemical information to stratify patients based on risk for metastasis, mortality, and biochemical failure, while also providing predictive information on the potential benefit of certain treatment modalities. In prostate cancer, the most studied and externally validated digital histopathology test is the ArteraAI Prostate.

ArteraAI Prostate incorporates digital biopsy images plus clinical information (baseline PSA, T stage, NCCN risk group, age, Gleason score) to provide prognostic and predictive information. Six phase III clinical trials were performed that looked at the prognostic value of this test. A meta-analysis of 1088 high risk patients in these trials showed that ArterAI Prostate was able to provide accurate and statistically significant information on 3 important prognostic values: Distant Metastasis (HR 1.9), Prostate Cancer Specific Mortality (HR 2.06), and Death with Distant Metastasis (HR 2.12).[63] Regarding predictive information, the ArteraAI Prostate model has been validated to differentiate which patients will benefit from certain treatment regimens. A study of 1192 patients compared the efficacy of long-term ADT versus short-term ADT in men with an AI predictive biomarker. The 15 year risk difference for distant metastasis in men with the biomarker was 14% when comparing long-term ADT (28 months) versus short-term ADT (4 months). Notably, there was no difference in the risk for distant metastasis in men that tested negative for the biomarker. In this study, 33% of the patients were negative for the biomarker, meaning that a substantial number of patients could have been saved from 24 extra months of ADT with the use of ArteraAI Prostate.[64]

In alignment with the research results on ArteraAI Prostate, the NCCN updated their guidelines to include recommendations on both the prognostic and therapeutic uses surrounding multimodal artificial intelligence (MMAI). Regarding prognostication, the current guideline reports that ArteraAI is superior to the standard pathologic and clinical models in terms of predicting distant metastasis and prostate cancer related mortality. Despite this, it is specifically noted that cut off thresholds have not been established to guide therapy, but instead can be used for more informed decision making. In terms of guiding therapy, the current guideline only addresses patients

Table 1
Available germline and somatic genetic testing

Mutation Type	Company	Panel Name	Included Genes	Tissue Sampling	Website
Germline Mutations	Myriad Genetics	myRisk Hereditary Cancer	ATM, BRCA1/2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, TP53	Blood Draw, Saliva	https://myriad.com/genetic-tests/myrisk-hereditary-cancer-test/
	Invitae	Hereditary Prostate Cancer Panel	EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, TP53	Blood Draw; Saliva; Buccal Swab; gDNA	https://www.invitae.com/providers/test-catalog/test-01362
	Ambry Genetics	CancerNext	40 Genes (eg, ATM, BRCA1/2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PTEN, TP53)	Blood Draw; Saliva; Buccal Swab	https://www.ambrygen.com/providers/genetic-testing/1/oncology/cancerext
Somatic Mutations	Foundation Medicine	FoundationOne CDx	324 genes (eg, ATM, BRCA1/2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51C, RAD51D, RAD54L, MSI)	Tumor Tissue	https://www.foundationmedicine.com/portfolio
		FoundationOne Liquid CDx	324 genes (eg, ATM, BRCA1/2, etc)	Blood Draw	https://www.foundationmedicine.com/portfolio
	Guardant Complete	Guardant360 Tissue	ATM, BRCA1/2, CDK12, CHEK1, CHEK2, FANCA, FANCL, MLH1, MRE11, NBN, PALB2, PTEN, RAD51B, RAD51C, RAD51D, RAD54L, RB1, TP53, MSI, TMB	Tumor Tissue	https://www.guardantcomplete.com/hcp
		Guardant360 CDx	ATM, BRCA1/2, CDK12, MLH1, PTEN, RB1, TP53, MSI, TMB	Blood Draw	https://www.guardant360.com

with intermediate risk prostate cancer planning to receive radiation therapy. If these patients are biomarker positive, a short-term ADT regimen is recommended, especially if they are in the unfavorable intermediate risk category. Conversely, if they are biomarker negative radiation therapy alone is sufficient.[28]

Plasma Circulating Tumor DNA

Plasma ctDNA are small fragments of DNA that have been released by tumor cells through the processes of apoptosis, necrosis, and secretion. Importantly, they contain the same somatic mutations that the tumor itself harbors essentially making it a "liquid biopsy" when measured. Currently, ctDNA is used for prognosis and disease response, but it is also used to look for actionable genetic variants. There is growing evidence for the early detection of prostate cancer using ctDNA, but this has shown to be limited with localized disease.[65]

Regarding prognosis, higher percentages of ctDNA found within plasma cell free DNA have independently shown to be associated with disease burden, progression free survival, and overall survival. One study found that patients with ctDNA% greater than 30 had a 5 times greater risk of PSA progression on first line therapy and a 5.6 times greater risk of death when compared with patients with a ctDNA% less than 2.[66] Similarly, shorter progression free survival and overall survival have been seen in mCRPC patients with persistently high levels of ctDNA following treatment with an ARPI. A multicenter observational study showed that going from detectable to undetectable ctDNA after treatment with an ARPI yielded a positive predictive value of 88% and negative predictive value of 92% when predicting which mCRPC patients would have a progression free survival greater than 6 months.[67]

ctDNA has also shown to effectively guide therapy due to its ability to detect actionable genetic mutations. The current NCCN guidelines recommend using ctDNA to test for somatic mutations in patients with metastatic prostate cancer, specifically when tissue biopsies are unsafe or not feasible. The intent of this is to look for somatic mutations in the homologous recombination, mismatch repair, and androgen receptor pathways. As outlined in the *Germline Mutations and Their Clinical Relevance* and the *Somatic Mutations and Their Clinical Relevance* sections above, certain mutations in these pathways have shown susceptibility to treatment with PARPis, PD-1 inhibitors, and ARPis (**Table 1**).

SUMMARY

Prostate cancer remains a highly prevalent disease that carries with it a disproportionate burden on the health care system, particularly in the non-Hispanic Black population. As a clinically heterogeneous disease, both germline and somatic genetic factors play a central role in shaping risk, guiding management, and informing prognosis. The increased understanding of these mutations has resulted in genetic testing serving an essential role for not only identifying individuals at increased risk, but also for selecting targeted therapies specific to individual mutations. Emerging tools such as PRS, digital histopathology platforms, tumor-derived GCs, and plasma ctDNA offer promising avenues for refining diagnosis, stratifying risk, and individualizing treatment. As these technologies advance and become increasingly integrated into clinical practice, a more personalized and precise approach to prostate cancer care is becoming possible, which has the potential to reduce mortality, limit overtreatment, and better identify those that may benefit most from targeted therapy.

DISCLOSURES

The authors have nothing to disclose.

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