Germline and Somatic Mutations in Prostate Cancer for the Clinician

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ABSTRACT

It is increasingly important for clinicians involved in the management of prostate cancer to understand the relevance of heritable (germline) mutations that, for select patients, affect prostate cancer risk and cancer biology, and acquired (somatic) mutations that occur in prostate cancer cells. In the advanced disease setting, mutations in homologous recombination repair genes (eg, *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *PALB2*) suggest candidacy for platinum chemotherapy and PARP inhibitor trials. Similarly, microsatellite instability and mismatch repair deficiency, which may arise in the setting of *MLH1*, *MSH2*, *MSH6*, and *PMS2* mutations, suggest potential vulnerability to PD-1 inhibitors. Germline genetic testing has potential importance in the treatment and assessment of familial risk, and tumor-directed somatic sequencing may guide treatment decision-making. This review provides clinicians with knowledge of basic genetic terminology, awareness of the importance of family history of cancer (not limited to prostate cancer), contrasts between the different but potentially related objectives of germline versus somatic testing of tumor tissue, and indications for genetic counseling. Specific clinical scenarios, objectives of testing, and nature of the assays are reviewed. Germline and somatic mutations of known and potential relevance to prostate cancer are discussed in the context of treatment options, and algorithms to assist clinicians in approaching this area are proposed.

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Expansion of genomic technologies and declining costs of next-generation sequencing (NGS) have led to rapid changes in germline and somatic genetic testing that must be considered in everyday clinical practice. Similar technology is used in direct-to-consumer “recreational” testing for understanding genealogic origins from an individual’s DNA. Tests for primary prostate cancer to determine risk of recurrence and inform decisions regarding active surveillance are addressed elsewhere.^{1–3} This review focuses on testing ordered by medical providers to determine heritable risk of cancer and guide treatment options in the advanced disease setting, provides a framework for understanding current options and uses for genetic testing, and considers data supporting genetic testing recommendations in the latest version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, version 2.2019 (in this issue).⁴

Germline DNA refers to the constitutional DNA of an individual resulting from the unique combination of genetic material, half from mother (egg) and half from father (sperm). (A list of key terms and definitions is provided in supplemental eTable 1, available with this article at JNCCN.org). Germline DNA is present in every cell of the body, and specific genetic changes have a 50/50 chance of being passed on to biologic children. Germline genetic testing can identify presence of inherited pathogenic variants (also called *mutations*) in genes associated with cancer risk. Testing can be performed on lymphocyte DNA from blood or a combination of lymphocyte and buccal cells from saliva, because germline DNA is nearly identical in all nucleated cells of an individual. Identification of a germline mutation associated with cancer susceptibility should involve a genetic counselor to ensure that medical, psychologic, legal, and ethical consequences for the patient and relatives are explained. Germline testing also can have important implications regarding treatment options for some patients with cancer.

In prostate cancer, the percentage of patients with germline mutations in DNA repair genes ranges from

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4.6% in localized disease to 11.8% to 16.2% in metastatic disease.^{5,6} Patients with a strong pattern of cancers found on a comprehensive family history should be evaluated by a genetic counselor, who may recommend specific tests (Figure 1). In addition, if a germline mutation is identified, genetic counselors ensure appropriate education and testing for family members who may also carry the same gene mutation, a process known as “cascade genetic testing.”

Sequencing DNA for tumor-acquired genetic changes (also referred to as *somatic mutations*) requires prostate tumor material: cancer-containing biopsies, surgical material, or, in some cases, circulating tumor cells or circulating tumor DNA (ctDNA) in the blood. Testing of

tumor tissue from primary or metastatic sites or blood may help guide treatment options in the advanced disease setting. A number of specific mutations are summarized in Table 1, although the base of knowledge is evolving rapidly.

Somatic mutations observed in tumor tissue may change over time due to genetic instability and selective pressure from therapy. Thus, repeat testing of tumor DNA may be appropriate during the disease course. Findings in archival primary tissue obtained years earlier may differ from those in a metastatic site, although detection of certain relevant mutations is possible early in tumorigenesis. Other potential limitations include

Figure 1. Algorithm for inherited/germline and tumor/somatic mutation testing in men diagnosed with prostate cancer.

Abbreviations: dMMR, mismatch repair deficiency; HRD, homologous recombination DNA repair; MSI-H, microsatellite instability-high; PV/LPV, pathologic variant or likely pathologic variant.

Table 1. Genes With Established or Emerging Potential Clinical Actionability, Germline vs Somatic

Gene	Association With Increased PC Risk	Prevalence of Germline Mutations in mPC ⁵	Prevalence of Germline Mutations in PC With Clinical Suspicion ¹¹	Consideration of DNA-Damaging Agents: PARPi Trials, Platinum ⁴⁰	Consideration of Immune Checkpoint Inhibitors: PD-1 Inhibitors
ATM	X	1.6%	2.0%	X	
ATR		0.3%	Not evaluated		
BRCA1	X	0.9%	0.7%	X	
BRCA2	X	5.4%	4.7%	X	
BRIP1		0.2%	0.3%		
CDK12 (somatic only)		—	—		X
CHEK2	X	1.9%	2.9%	X	
FAM175A		0.2%	Not evaluated		
FANCA		—	Not evaluated	X	
HOXB13 (germline only)	X	Not evaluated	1.1%		
MLH1	X	—	0.06%		X
MRE11A		0.14%	Not evaluated		
MSH2	X	0.14%	0.69%		X
MSH6	X	0.14%	0.45%		X
NBN	^a	0.3%	0.32%	X	
PALB2	^a	0.4%	0.56%	X	
PMS2	X	0.3%	0.54%		X
RAD51C		0.14%	0.21%		
RAD51D		0.4%	0.15%		

Abbreviations: mPC, metastatic prostate cancer; PARPi, PARP inhibitors; PC, prostate cancer.

^aEmerging/Limited data.

variance in tumor content and purity, and sensitivity and specificity of detecting tumor-specific mutations. Tumor-based testing has the potential to identify germline mutations that have implications for inherited cancer predisposition.^{7,8} Tumor testing should never be used to substitute for germline testing because of the risk for false-positives and false-negatives due to variation in bioinformatics and reporting between commercially available tests. If somatic testing identifies a mutation in a gene associated with cancer predisposition (eg, *BRCA2*), referral to a genetic counselor for dedicated, confirmatory germline testing is indicated.

Family and Personal History of Cancer

Family history of cancer remains a foundation of genetic risk assessment, and inquiring about prostate and non-prostate cancers is critical to a complete assessment for possible inherited cancer risk (supplemental eTable 2).⁵ In particular, cancers of the breast (especially in men or those diagnosed at a young age), ovary, pancreas, and melanomas should be noted, given their known association with mutations in *BRCA1/2*.⁹ However, other cancers, such as mesothelioma, should also be noted.¹⁰

Importantly, family history is necessary but not sufficient for identifying all germline carriers.⁵

In a recent study of 3,607 men diagnosed with prostate cancer who underwent genetic testing between 2013 and 2018, 17.2% were found to have germline mutations and 37% would not have met criteria for testing from the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.⁹ However, the dates spanned a period when guidelines were changing (consideration of genetic testing in individuals with a personal history of metastatic prostate cancer was not incorporated until 2017), and therefore the tested population was likely influenced by clinical suspicion based on family history even if they did not meet contemporaneous testing guidelines.¹¹ The argument that all men with prostate cancer should be tested is thought-provoking, but cost-effectiveness and actionability of widespread genetic testing in early, low-risk prostate cancer settings without other risk factors remain unclear, and short-term unintended consequences include clinical confusion and low-yield depletion of limited genetic counseling resources.

In contrast, clinical predictors of germline status, such as metastatic stage⁵ or intraductal histology,^{12,13}

emerging data about ductal histology,^{14,15} and/or history of second or multiple primary cancers at younger age¹⁶ may help prioritize candidates for testing, because each has been independently associated with the presence of germline DNA repair mutations. The biochemically recurrent population is heterogeneous, although application of advanced modern imaging such as C-11 choline and F-18 fluciclovine PET scans may help distinguish patients with indolent versus occult metastatic disease. Figure 1 illustrates the interaction between clinical disease features, family history, and pathology to determine who should be offered germline and/or somatic testing and genetic counseling.⁴

Genetic Counseling

Genetic counselors play an essential role in many aspects of the genetic testing process, but particularly in educating patients and family members, deciding on appropriate testing when there is strong family history, guiding accurate communication of medical information to family, and addressing psychosocial aspects of testing.

Risk assessment and pretest genetic counseling have been performed traditionally by genetic counselors, but access and long wait times can hamper time-sensitive testing that may inform treatment options in advanced disease. Ongoing studies are exploring novel delivery models for genetic services to balance time sensitivity with responsibility for informed consent, pretest education, and posttest follow-up (ClinicalTrials.gov identifiers: NCT02987543, NCT3328091, and NCT03503097).

Figure 1 illustrates the points in care at which genetic counseling is essential: (1) when there is a strong family history of cancer to ensure appropriate testing is ordered and that posttest communication to family is accurate; (2) after a germline pathogenic variant (mutation) is identified to ensure cascade testing; (3) when somatic testing uncovers a mutation that is potentially germline in nature; or (4) if the patient displays any indication of stress, distress, or unanswered questions. Providers should work closely with their genetics colleagues to develop systems that address patient needs with thoughtful stewardship of local genetics resources.

Genetic Testing

Choice of which germline test to use is beyond the scope of this review, although a number of commercial tests are available and typically use blood or saliva. There is variation in insurance coverage and out-of-pocket costs, although with assistance programs and competitive pricing, patient costs can often be limited to several hundred dollars or less. If genetic testing is being performed in the context of advanced prostate cancer, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* should be included due to potential

treatment implications, although this list is expected to be refined over time. In specific research or clinical contexts, a larger gene panel may be appropriate. For example, *HOXB13* is a prostate cancer risk gene that does not have clear therapeutic implications in advanced disease at this time, but which should be included if heritable prostate cancer risk is part of the question.⁴ Similarly, the gene list to consider may be larger for a somatic tumor gene panel and extend beyond cancer risk genes.

Potential outcomes for germline testing include identification of a mutation (pathogenic or likely pathogenic variant), which may suggest additional prostate cancer treatment options and clinical trials and inform risk of other cancers. This result would also indicate a 50/50 chance that first-degree relatives inherited the same risk gene and thus would prompt a recommendation for the patient to share this information (including a copy of test results) with relatives and for referral of family members to genetic counseling for cascade genetic testing. Single-site testing for a specific mutation is typically covered by insurance and is less expensive.

Another potential outcome is a variant of uncertain significance (VUS), which indicates that available data in the field were insufficient to characterize the finding as either benign or pathogenic at the time of test interpretation. A VUS result should not be used to direct clinical management. Research studies are available to help reclassify VUS, and these can be discussed with a genetic counselor.¹⁷ In one study, 7.7% of VUS results were reclassified: 91% as benign/likely benign and 9% as pathogenic/likely pathogenic.¹⁸

An outcome could also be that no mutations were identified (a benign result). Failure to identify a single, inherited cancer risk–associated mutation does not obviate an increased risk of prostate cancer to family members if there is a strong family history. If testing is negative (benign, with no mutations) or identifies a VUS, the clinical family history should be used to guide cancer screening for family members. Although tempting, VUS—including and especially in *BRCA1/2*—should not be used for medical management, although follow-up with genetic counseling and consideration of research opportunities, such as registries and variant reclassification studies, are encouraged.

Individuals found to have germline pathogenic (or likely pathogenic) variants must see a genetic counselor for counseling, guidance on communication to family, and appropriate cascade genetic testing that extends genetic testing to other family members (<https://www.nsgc.org/findageneticcounselor>). Providers should also be aware that telehealth-, phone-, and new technology-based genetic counseling services may be an additional option for patients.

Genes With Germline and Somatic Actionability

Prostate Cancer Risk

For germline *BRCA2* mutation carriers, the relative risk of developing prostate cancer by age 65 years is estimated to be 2.5- to 8.6-fold compared with noncarriers.¹⁹ In a recent study, lifetime risk of prostate cancer by age 80 years was reported between 19% and 61%, and 7% and 26% for carriers of *BRCA2* and *BRCA1* mutations, respectively.²⁰ Retrospective studies have shown that men with *BRCA2* mutations present at a younger age with higher Gleason grade tumors, higher rates of nodal involvement and distant metastases at diagnosis, and higher prostate cancer–specific mortality.^{21,22} *BRCA1*,²³ *ATM*,²⁴ *CHEK2*,^{25,26} and *PALB2*²⁷ also are involved in homologous recombination DNA repair and have been associated with increased prostate cancer risk, although these germline mutations have fewer data available and suggest less apparent relative risk of developing prostate cancer compared with *BRCA2*.^{5,28} Germline mutations in the mismatch repair (MMR) genes *MLH1*, *PMS2*, *MSH2*, and *MSH6* are associated with Lynch syndrome, an inherited condition that predisposes individuals to an increased risk of developing many different types of cancers, including colorectal, endometrial, and gastrointestinal, often at a young age.²⁹ Several studies suggest a modest increased risk of prostate cancer in patients with Lynch syndrome,^{30,31} and germline MMR gene mutations have been seen in the metastatic setting.⁵ *HOXB13* G84E is a germline variant associated with increased risk of developing prostate cancer, but this variant is not clearly associated with increased disease aggressiveness nor should it influence treatment decision-making.^{32–34} Emerging data suggest that *NBS1* (also called *NBN*),³⁵ *FANCA*,³⁶ and other DNA repair genes are associated with increased prostate cancer risk and choice of treatment, but further studies are needed before clinical action is warranted.

Screening Recommendations for Carriers of Pathogenic Germline Mutations

Screening recommendations have not been established for men with pathogenic germline mutations associated with increased prostate cancer risk. The ongoing IMPACT study is evaluating the role of targeted prostate-specific antigen (PSA) screening in men with *BRCA1/2* mutations (ClinicalTrials.gov identifier: NCT00261456). Preliminary results support yearly PSA screening in men with *BRCA2* mutations aged 40 to 69 years.³⁷ NCI's recently opened Men at High Genetic Risk for Prostate Cancer trial incorporates annual PSA testing and regular digital rectal examination and prostate MRI (NCT03805919). If clinical trial participation is not available, annual PSA measurement for carriers of high-risk mutations should begin at age 40 years (Figure 2). Men with PSA levels greater than the

median age-adjusted PSA ranges^{3,38,39} may consider prostate biopsy, which may be MRI/ultrasound fusion–guided.

Therapeutic Implications of Genetic Testing

Prostate tumors can now be sequenced for mutations that may offer molecularly targeted therapeutic options.⁴ Archival tissue from the primary is often considered acceptable for studies of targeted agents when the biomarker in question is present, but archival tissue from a patient who has had multiple therapies may not reflect current tumor DNA status. Contemporary sampling of metastatic disease sites or cell-free ctDNA or circulating tumor cells may be more informative, although uninformative somatic testing, false-negatives, and limitations due to tumor purity must also be considered. Studies suggest that concordance with metastatic tissue can be good,⁴⁰ and that clinical selection and the timing of ctDNA draw at progression may improve diagnostic yield.⁴¹

Recent studies have resulted in major changes to consideration of germline testing in some patients with prostate cancer.^{5,6,13,15} Germline genetic testing is now recommended for all men with a family history of prostate cancer or intraductal histology and/or high- or very high-risk regional or metastatic prostate cancer.⁴ The decreasing cost of germline panel testing has made it more feasible to follow these guidelines for testing, although substantial issues remain regarding disparities in insurance coverage and access to genetic counseling.

The standards for somatic testing and reporting are less established than those for germline testing. Rapid changes in assays and clinical trials in progress make it difficult to recommend specific assays. A number of NGS sequencing panels are available and FDA-approved for somatic testing

For men with personal history of *BRCA1/2* mutation, Lynch syndrome, or mutations (ie, pathogenic variants) in prostate cancer-associated risk genes:

- Begin screening at age 40 y.
- Annual PSA and DRE.
- Men with a PSA level above the median for their age group are at higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk.
- If PSA level is below age-adjusted median and no other indication for biopsy, repeat screening in 12 months.
- If PSA level is above age-adjusted median, recheck PSA in 6–12 months; if increased, consider extended pattern biopsy with mpMRI or TRUS-guidance.
- Upper limit age-adjusted median range PSA^{38,39}:
 - Aged ≤49 y, PSA >1.5 ng/mL
 - Aged 50–59 y, PSA >2.0 ng/mL
 - Aged 60–69 y, PSA >2.5 ng/mL

Figure 2. Recommendations for prostate cancer early detection in carriers of high-risk mutations.

Abbreviations: DRE, digital rectal examination; mpMRI, multiparametric MRI; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

in CLIA-certified laboratories. Currently, somatic testing for homologous recombination gene mutations and microsatellite instability (MSI) and MMR deficiency (dMMR) should be considered due to potential treatment implications. In addition, some somatic NGS assays may also report alterations that, although investigational, may inform clinical trial candidacy: androgen receptor amplifications, *PTEN* deletions, PI3K/Akt/mTOR pathway alterations, and *TPR2-ERG* gene fusions.

The definition of actionability for specific gene mutations in prostate cancer is emerging, and currently at least 2 classes of gene mutations should be considered (Table 1). Tumor and/or germline mutations in genes such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, and *CHEK2* may suggest candidacy for early use of platinum-based chemotherapy^{42,43} or enrollment in clinical trials testing PARP inhibitors,⁴⁴ such as olaparib and rucaparib, which have been granted breakthrough designation by the FDA. Ongoing clinical trials are evaluating a number of PARP inhibitors for metastatic castration-resistant prostate cancer (mCRPC) and earlier disease states (ClinicalTrials.gov identifiers: NCT02854436, NCT02975934, NCT02987543, and NCT03148795). Retrospective and prospective studies to date have not shown that any FDA-approved treatment of mCRPC should be withheld from men with advanced prostate cancer and germline mutations.^{45–47}

Tumor DNA evaluation for high MSI (MSI-H) or dMMR can be determined using immunohistochemistry or NGS methods demonstrating loss of function of *MLH1*, *MSH2*, *MSH6*, or *PMS2*, and is ideally validated for prostate cancer.^{48,49} Identification of tumor MSI-H or dMMR indicates potential eligibility for pembrolizumab in later lines of therapy for advanced disease.⁴

Importance of the Molecular Tumor Board

Because approaches to NGS testing of tumors have changed and continue to evolve quickly, interpretation of results for the busy clinician may be challenging. Many institutions have instituted molecular tumor boards in which relevant clinical information is presented alongside results of germline and/or somatic testing and is reviewed by a multidisciplinary team. These tumor

boards should include expert interpretation of data by a molecular pathologist, medical oncologist with disease-specific expertise, and genetic counselor, and may also include radiation and surgical oncologists. Such molecular tumor boards are increasingly available at comprehensive cancer centers with consultation for or participation by outside physicians because molecular pathology expertise is not yet widely available.

Conclusions

A summary of important points is available in eTable 3. Information about heritable (germline) and tumor-acquired (somatic) mutations has increasing importance in the management of men with prostate cancer. Germline data can inform both patient and family risk for prostate and other cancers and drive more aggressive screening in men at high risk of developing prostate cancer. Somatic testing is performed to determine whether the tumor has actionable targets for therapy, and prior knowledge of germline mutations can help in the interpretation of the results. Molecular tumor boards are needed to best interpret results and to direct clinical management and trial opportunities for providers and patients. Partnership with genetic counselors is needed to assist patients and relatives with decisions regarding genetic testing, interpretation, and follow-up cascade testing for family members. Clinicians should be aware of how to integrate genomic testing into treatment paradigms, because this field is rapidly evolving.

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Germline and Somatic Mutations in Prostate Cancer for the Clinician

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eTable 1: Key Terms and Definitions

eTable 2: Obtaining a Comprehensive Family History of Cancer

eTable 3: Take-Home Points

eTable 1. Key Terms and Definitions

Cascade testing: Genetic counseling and testing in blood relatives of individuals who have been identified with specific genetic mutations; may include screening, counseling, or referral for a patient with a relative who has tested positive for a genetic mutation.
CTC: Circulating tumor cells. Tumor cells from the circulation (blood) that can be enumerated, measured, and/or evaluated.
ctDNA: Circulating tumor DNA. Typically measured from cell-free DNA in the plasma.
DDR: DNA damage response pathways. Includes homologous recombination, MMR, base excision repair, and others.
dMMR: Deficiency in mismatch repair. Refers to the inability to use a mechanism of correcting errors in DNA by detecting and replacing bases in the DNA that are paired incorrectly (mismatched bases). dMMR in the tumor may be associated with susceptibility to treatments, such as immune checkpoint inhibitors.
Genetic counseling: The evaluation and understanding of a family's risk for an inherited medical condition. A genetic counselor is a healthcare professional with specialized training in medical genetics and counseling.
Genetic testing: Laboratory methods to evaluate DNA of an individual to identify increased risks of specific conditions (eg, cancer), select treatment, or determine response to treatment.
Germline DNA: Constitutional DNA that is inherited from mother and father, present in nucleated cells of the body, such as lymphocytes, and may be passed on to children. Some genes may be shared with siblings.
HRD: Homologous recombination deficiency. Refers to the inability to use a common mechanism of repairing harmful breaks that occur on both strands of DNA, known as doublestrand breaks, through genetic recombination. Examples: <i>BRCA2</i> , <i>BRCA1</i> , <i>PALB2</i> .
MSI-H: Microsatellite instability. MSI-high refers to microsatellite instability, a measure of dMMR. Can result from defects in genes such as <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , or <i>PMS2</i> .
NGS: Next-generation sequencing. High-throughput DNA sequencing technologies. Millions or billions of DNA strands can be sequenced in parallel to yield more throughput. Practically, this allows multiple genes to be tested at the same time in gene "panels."
Pathogenic variant: A genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder (eg, prostate cancer). Development of prostate cancer is more likely, but not certain, when such a variant (or mutation) is inherited.
Somatic DNA: Acquired mutations and genetic changes to the germline DNA. Often refers to tumor-associated genetic changes that are not heritable.
VUS: Variant of uncertain significance. Typically refers to a genetic change in germline DNA where there is insufficient information available to know if it causes an increased susceptibility to cancer or not.

Abbreviations: CTC, circulating tumor cells; ctDNA, circulating tumor DNA; dMMR, mismatch repair deficiency; HRD, homologous recombination deficiency; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability–high; NGS, next-generation sequencing; VUS, variant of uncertain significance.

eTable 2. Obtaining a Comprehensive Family History of Cancer
Detailed family history includes: <ul style="list-style-type: none">• Parents• Children• Siblings/Half siblings• Grandparents and great-grandparents (specify maternal or paternal)• Nieces and nephews• Aunts and uncles (specify maternal or paternal)• Cousins (specify maternal or paternal)• Ethnicity/Country of origin• Consanguinity
Minimal data for each cancer-affected relative: <ul style="list-style-type: none">• Current age and age at diagnosis (if not known exactly, decades can be helpful)• Age at and cause of death (especially if cancer-related)• Type of cancer (note multiple primaries)• Results of any prior genetic testing
Resources for collecting family history: <ul style="list-style-type: none">• CDC My Family Health Portrait, https://phgkb.cdc.gov/FHH/html/index.html• Cancer.net, https://www.cancer.net/sites/cancer.net/files/cancer_family_history_questionnaire.pdf• NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (see algorithm page HRS-A; available online at NCCN.org).

Abbreviation: CDC, Centers for Disease Control and Prevention.

eTable 3: Take-Home Points

<ul style="list-style-type: none"> • Germline DNA is inherited from both biologic parents and is present in all cells in the body. It does not change over time, therefore repeat testing will typically be of limited value.
<ul style="list-style-type: none"> • Somatic (tumor) DNA is comprised of germline genetic material with additional acquired mutations; however, somatic testing platforms may or may not report suspected germline mutations (pathogenic variants).
<ul style="list-style-type: none"> • Tumor testing may suggest the need for, but should never replace, dedicated germline testing.
<ul style="list-style-type: none"> • Tumor evolution over time means repeat somatic testing may be of value.
<ul style="list-style-type: none"> • Germline testing can identify increased risk for heritable cancers.
<ul style="list-style-type: none"> • Germline DNA may have therapeutic implications for some patients.
<ul style="list-style-type: none"> • Tumor sequencing can be performed to find actionable mutations that may have therapeutic implications in advanced disease.
<ul style="list-style-type: none"> • Germline mutation testing should be offered to patients with a family history of prostate other cancers, or those with a personal history of high- and very high-risk localized prostate cancer, regional, or metastatic disease.
<ul style="list-style-type: none"> • All patients with pathogenic germline mutations should be referred to a genetic counselor.
<ul style="list-style-type: none"> • When there is a strong family history, genetic counseling is recommended before genetic testing whenever possible.
<ul style="list-style-type: none"> • If germline testing is negative or inconclusive (ie, there is no known cancer associated with the identified mutation) but there is a strong family history for cancers, referral to genetic counseling is indicated.
<ul style="list-style-type: none"> • Variants of uncertain significance (VUS; including in <i>BRCA1/2</i>) should not be used for medical management.
<ul style="list-style-type: none"> • Tumor DNA analysis should be performed at a time when a new therapy is under consideration.
<ul style="list-style-type: none"> • Intraductal histology has a higher association with actionable tumor and germline mutations.
<ul style="list-style-type: none"> • Genetic counselors can be found at https://www.nsgc.org/findageneticcounselor.
<ul style="list-style-type: none"> • Carriers of the <i>BRCA1/2</i> mutation are at increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline <i>BRCA2</i> mutations occurs earlier and is more likely to be associated with prostate cancer mortality.
<ul style="list-style-type: none"> • Men with germline <i>BRCA1/2</i> mutations may consider beginning shared decision-making about PSA screening at age 40 years and at annual intervals, factoring in age-adjusted median PSA values. Early detection clinical trials are recommended whenever possible.