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Germline Testing for Prostate Cancer

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to identify the rationale for and appropriately select prostate cancer patients for germline testing.

This AUA Update aligns with the American Board of Urology Module on Oncology, Urinary Diversion and Adrenal. Additional information on this topic can be found in the AUA Core Curriculum section on Oncology—Prostate.

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INTRODUCTION

It is estimated that 248,530 cases of prostate cancer (PCa) will be diagnosed in 2021 in the United States, and that PCa will result in 34,130 deaths.[1] While organ-confined disease, which represents the bulk of new PCa diagnoses, has a reasonably high expectation of cure (nearly 100% 5-year cancer-specific survival), metastatic PCa has a poor 5-year cancer-specific survival rate of ~31%.[2] As such, it is critical to understand the role that inherited factors play in the development of lethal PCa. Most lethal PCa is due to relapse on and failure of androgen deprivation therapy (ADT), which serves as the first-line therapeutic strategy for disseminated PCa.[3] ADT diminished the activating ligand for the androgen receptor (AR), which drives critical cancer phenotypes including cancer cell proliferation and DNA damage repair. ADT fails when AR function is reactivated, and this stage of disease is termed castration-resistant prostate cancer (CRPC). Metastatic CRPC (mCRPC) is responsible for the majority of cancer-specific deaths in PCa. There is currently no durable cure for patients with mCRPC.[3]

Germline genetic testing seeks to identify inherited mutated genes that increase cancer risk in the individual or their immediate family members. Utilizing germline genetic testing to identify potentially lethal PCa and better risk stratify men is a valuable asset in the management of PCa. Germline genetic testing has the potential to impact PCa screening, prognosis, and treatment options for men with PCa. A related topic is somatic tumor genetic testing that identifies unique mutated genes in the tumor or metastasis that may be spontaneous or may be the result of inherited mutated genes. Somatic testing is used to guide standard or investigational agents in the treatment of advanced disease.

Based on prior epidemiologic studies, including twin studies,[4,5] the heritable component of PCa has been long-established. Having a first-degree relative with PCa confers a 2–4 fold increased risk of developing PCa,[6] while having a first-degree relative with lethal PCa confers a 2–3 fold increased risk of PCa-associated death.[7] Five to 10% of PCa can be characterized as hereditary, 15%–20% as familial, and 70%–80% is considered to be sporadic. Genome-wide association studies have identified ~170 single-nucleotide polymorphisms associated with PCa risk.[8] However, while these single-nucleotide polymorphisms are of high prevalence in this patient population, their penetrance, and therefore clinical impact, remain low. Individually, these single-nucleotide polymorphisms do not appear to result in a significant increase in PCa risk, but cumulatively, their effect is more significant. While these single-nucleotide polymorphisms are certainly important to the biology of PCa, the purpose of this review will be to discuss the impact of germline testing for high penetrance gene mutations on PCa risk, disease severity and treatment. This is due to the relatively recent advancements in our understanding of the importance of germline testing in PCa.[9–11]

GERMLINE ALTERATIONS ASSOCIATED WITH PCa RISK AND AGGRESSIVENESS

In a landmark study by Robinson et al, the authors first identified that 8% of mCRPC tumors harbor actionable germline alterations,[12] the majority of which occur in DNA repair genes.[13] Properly functioning DNA repair genes such as BRCA1/2, ATM, and others maintain cellular stability and properly repair DNA breaks. **Germline DNA repair gene mutations have been identified at a significantly higher rate in metastatic PCa (11%–33%) than primary PCa (approximately 5%).[13,14]** Germline mutations in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, and *NBN* are associated with increased risk of developing PCa.[15–31] With the exception of *HOXB13*, each of these genes is involved in DNA damage repair. It should be stressed that these identified mutated genes are not the cause of PCa but can engender more aggressive forms of the disease. Germline mutations in *HOXB13* and *BRCA2* have the strongest association with PCa development (see table 1). **Germline mutations in the DNA repair genes *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, *NBN*, and *PALB2* also confer an increased risk of aggressive PCa;[28–30,32–54]** in particular, the greatest risk is men with germline *BRCA2* mutations. It is hypothesized that the enrichment of DNA repair gene mutations in PCa facilitates further mutational events that drive PCa carcinogenesis and disease progression.

Despite African American men being more likely to develop PCa and having worse disease outcomes than other racial/ethnic groups, germline mutations in DNA repair genes are less prevalent in African American than Caucasian PCa men.[55] Individuals who harbor these common mutated PCa germ line genes have increased risk for other tumors including male breast cancer, pancreatic cancer, melanoma and Lynch syndrome related gastro-intestinal tumors.[17] Further, if these mutations are inherited by close female relatives, their risk increases dramatically for developing breast and ovarian cancer; along with increased risk for pancreatic cancer, melanoma, and other tumors such as gastro-intestinal cancers noted for males. **Cascade testing, which is a systematic process for the identification of individuals at risk in the family for a hereditary condition beginning with identification of an individual with the condition, may be appropriate in certain settings and is usually best evaluated by a trained genetic counsellor.** The presence of hereditary cancer syndromes in the family such as Hereditary Breast and Ovarian Cancer syndromes may be considered in PCa screening decisions. This underscores the potential importance of germline genetic testing in the management of PCa for the patient and their families. Note that at the present time if the male identified with aggressive or metastatic PCa undergoes genetic testing and does not have an identified mutation cascade, testing of additional family members is generally not recommended.

COMMERCIALLY AVAILABLE GERMLINE GENETIC TESTING FOR PCa

Molecular studies have become the mainstay of what is termed precision medicine. Given the relative ease of sample

ABBREVIATIONS: androgen deprivation therapy (ADT), androgren receptor (AR), castration resistant prostate cancer (CRPC), family history (FH), metastatic CRPC (mCRPC), poly (ADP ribose) polymerase (PARP), prostate cancer (PCa)

procurement and ever-decreasing cost of next generation molecular sequencing, germline testing using commercial reference labs is becoming commonplace. As outlined in figure 1, there are several general approaches to molecular testing in PCa. Molecular characterization of PCa biopsy material has been used for several years to identify gene expression patterns of selected and proprietary gene panels. These proprietary assays have been used primarily for the determination of PCa outcome measures such as final pathology, PCa recurrence or PCa- specific death or in further identification of undetected cancer on prostate biopsy.[56] Genomic somatic tumor sequencing (middle panel) involves the use of either primary tumor tissue, metastasis or material derived from liquid biopsy (circulating tumor cells in blood, cell-free DNA etc). This somatic genomic tissue testing screens for large panels of mutated genes. Somatic tissue genomic testing has been traditionally used in oncology to screen patients for potentially actionable genes when using experimental agents. Most relevant to this AUA Update, inherited cancer risk testing using germline genetic testing (Figure 1, right panel) involves the use of either a buccal swab or a blood draw. The sample undergoes targeted sequencing of distinct gene panels often associated with PCa with the goal of identifying any inherited mutated genes.

As outlined in table 2, a number of commercial labs are currently performing PCa-specific targeted gene panel sequencing, with the genes included on each panel shaded in grey. As will be discussed below, currently there is no definitive evidence that every gene on each panel will provide actionable information, from screening, family cascade testing or therapeutic options. Choosing which commercial genetic testing assay to use can be based on physician familiarity with the assay, reimbursement schema and/or enterprise-level agreements. In general, traditional Medicare enrollees will have coverage for genetic testing with the following: personal and family history (FH) of ≥3 family members with breast, pancreatic, and/or prostate (Gleason ≥7 or metastatic disease) cancer. Coverage by commercial insurance carriers varies by company and specific policy language. Many of these commercial laboratories will provide basic genetic counselling if abnormalities are identified and many companies work with individuals to limit out-of-pocket expenses.

APPROPRIATE USE OF GERMLINE TESTING FOR PCa

Based on the most recent National Comprehensive Cancer Network® guideline, germline genetic testing guidelines for primary PCa include:[57]

- **For risk groups Very Low, Low, and Intermediate, germline testing is recommended if the patient has a significant FH of cancer (PCa OR[3] family members on the same side with related malignancies such as breast cancer, ovarian cancers, melanoma, pancreatic cancer or gastro intestinal cancers related to Lynch syndrome) or their tumor has intraductal/cribriform histology.**
- **In contrast, men with High and Very High risk localized PCa or any metastatic PCa are recommended for germline testing, irrespective of FH or histology.**

The most recent AUA guidelines endorse less comprehensive indications for germline genetic testing, recommending testing:

- **For all men with metastatic PCa, regardless of FH or histology.**
- **For men with localized high-risk PCa, particularly in men with family history of first degree relative with cancers of the breast, ovary, pancreas, other gastrointestinal cancers, or lymphoma.**

Somatic tumor sequencing is also becoming important and may inform the need for germline genetic testing. During the

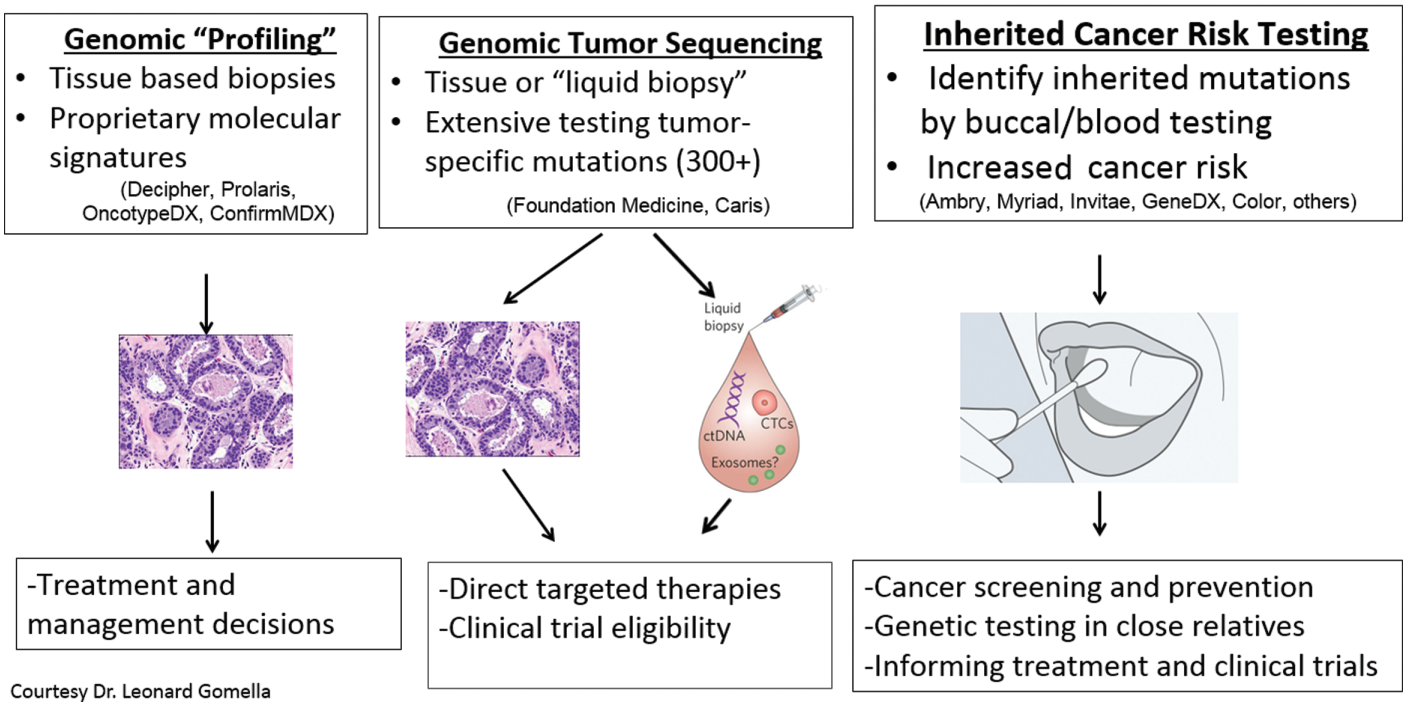

Figure. Various genetic and genomic molecular tests used in management of PCa. Assay names identified are property of various commercial entities and are noted for educational purposes and do not imply any endorsement. Figure created by Dr. Gomella.

second Philadelphia Prostate Cancer International Consensus Conference in 2017,[11] experts endorsed expanded indications for germline genetic testing to include:

- **Men with FH of metastatic PCa (not just PCa death) and**
- **Men with two or more cancers in the Hereditary Breast and Ovarian Cancer syndromes or Lynch syndrome spectrum in any relatives on the same side of the family (especially if diagnosed at age <50).**

Choice of panel and gene prioritization was also considered at the Philadelphia Prostate Cancer Consensus Conference.[11] The consensus results are outlined in table 3.

GERMLINE AND SOMATIC TESTING TO DIRECT PATIENT CARE (PRECISION MEDICINE)

In addition to determining increased cancer risk in individuals and in their families, testing for mutated genes (germline or somatic) is now being used to direct treatment of advanced disease. The first indication using this approach was the use of pembrolizumab in any solid tumor, including PCa, with microsatellite instability-high or mismatch repair deficient tumors based on tissue or liquid biopsy for these somatic alterations.[58] **The May 2020 Food and Drug Administration approval of the poly (ADP-ribose) polymerase (PARP) inhibitors olaparib and rucaparib for the treatment of mCRPC was an important development in precision medicine for PCa.[59]** The PARP inhibitors olaparib and rucaparib, used in other cancers such as breast and ovarian, are now available for patients with mCRPC with germline or somatic BRCA1/2 alterations or other DNA repair pathway mutated genes who have failed other therapies such as AR/synthesis pathway inhibitors or chemotherapy.[59] The AUA/ASTRO/SUO 2021 advanced PCa guidelines initially released in 2020 stated the following:[60,61]

> "Clinicians should offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. Platinum based chemotherapy may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor."

Finally, use of germline genetic testing to inform PCa management was considered at the Philadelphia Prostate Cancer Consensus Conference.[9] The results are outlined in table 4.

CONCLUDING REMARKS

As germline genetic testing for PCa becomes more frequently utilized, 1) appropriate genetic counseling, pre- and post-testing, is a critical component of the process,[62–67] yet the current genetic counselor workforce is unable to meet the demands of the projected referral volume;[68–70] 2) health care providers who are not formally trained in genetics, including urologists, will need to be rapidly educated on the proper use of genetic testing and are encouraged to collaborate with genetic counselors; 3) based on the number of "Consider" results outlined in tables 3 and 4 within this Update, it is clear that further evidence is needed to make more robust recommendations with respect to germline testing in PCa; and 4) germline and somatic tumor testing in the context of PCa will continue to evolve to include screening, prognosis, and treatment decision in PCa patients.

DID YOU KNOW?

- Germline genetic testing is being increasingly utilized in PCa.
- Germline genetic testing has been identified as an important factor in screening for PCa if a familial hereditary gene mutation is identified.
- Urologists should expand questioning PCa patients about FH beyond this disease to include breast, ovarian and pancreatic cancers, melanoma and gastrointestinal cancers.
- Most germline mutations in metastatic PCa patients occur in DNA damage repair genes such as BRCA1/2.
- The identification of mutated germline and other genes now may direct therapy of advanced disease.
- Testing the tumor or metastasis for somatic (non-inherited) mutations may also direct therapy of advanced mCRPC.

Table 1. Some genes that are commonly mutated in inherited germline PCa

Gene	PCa Risk	Mechanism
ATM	Elevated	DNA damage response
BRCA1	~20%	DNA damage repair
BRCA2	~20%	DNA damage repair
CHEK2	Elevated	DNA repair through phosphorylation of BRCA2
EPCAM	Up to 30%	Upregulate c-myc
HOXB13	Up to 60%	AR repressor
MLH1	Up to 30%	DNA repair
MSH2	Up to 30%	DNA repair
MSH6	Up to 30%	DNA repair
NBN	Elevated	DNA repair
PMS2	Up to 30%	DNA mismatch repair
TP53	Unknown	Tumor suppressor
PALB2	Preliminary	Tumor suppressor
RAD51D	Preliminary	DNA repair

Most genes are associated with DNA repair pathways. HOXB13 gene (AR pathway) is highlighted as gene linked with certain cases of clearly defined inherited PCa (younger, high grade, multiple males). Based on data from https://www.ncbi.nlm.nih.gov/gene/.[71]

Table 2. Commercially available PCa-specific genetic testing panels that are commonly used

	Ambry Genetics	Fulgent	GeneDx	Invitae
	"ProstateNext"	"Prostate Cancer Comprehensive Panel"	"Prostate Cancer Panel"	"Prostate Cancer Panel"
ATM	✓	✓	✓	✓
ATR				
BAP1				
BARD1				
BRCA1	✓	✓	✓	✓
BRCA2	✓	✓	✓	✓
BRIP1				
CHEK2	✓	✓	✓	✓
EPCAM	✓	✓	✓	✓
FAM175A				
GEN1				
HOXB13	✓	✓	✓	✓
MLH1	✓	✓	✓	✓
MRE11A				
MSH2	✓	✓	✓	✓
MSH6	✓	✓	✓	✓
NBN	✓	✓	✓	✓
PALB2	✓			
PMS2	✓	✓	✓	✓
RAD51C				
RAD51D	✓			
TP53	✓	✓	✓	✓
XRCC2				

Check mark denotes if gene is included in specific gene panel. Not all genes noted have been fully characterized in PCa. Other commercial assays are more broadly based for detection of many cancers that include known PCa mutated genes (eg "myRisk" by Myriad, "Hereditary Cancer Test" by Color). Assay names identified are property of various commercial entities and are noted for educational purposes only and do not imply any endorsement.

Table 3. Germline genetic testing parameters based on expert panel recommendations at the 2017 Philadelphia Prostate Cancer International Consensus[11]

	Recommended Panel	Priority Germline Testing					Additional Genes Based on Personal or Family History
		BRCA2	BRCA1	DNA mismatch repair genes (*MSH2, MSH6, MLH1, PMS2*)	*ATM*	HOXB13	
Metastatic PCa	Comprehensive (large) panel to determine eligibility for therapy or clinical trials	Recommend	Recommend	Recommend	Consider		Recommend
Localized PCa	Reflex testing may be optimal (Defined as initial set of genes tested followed by broad panel)	Recommend			Consider		Recommend
Men without PCa meeting FH testing criteria	Reflex testing may be optimal	Recommend	Consider		Consider	Recommend	Recommend

Shading key: orange for consider, green for recommend.

Table 4. Germline genetic testing parameters and PCa management, based on expert panel recommendations at the 2017 Philadelphia Prostate Cancer International Consensus[11]

Context	Considerations	Expert Consensus for Germline Testing
Metastatic PCa	Enrollment in precision medicine trials	Recommend
	BRCA2 to inform response to PARP inhibitors	Recommend
	BRCA1 to inform response to PARP inhibitors	Consider
	BRCA2 to inform response to platinum-based chemotherapy	Consider
	BRCA1 to inform response to platinum-based chemotherapy	Consider
	PARP inhibitor rather than taxane after progression on abiraterone with DNA repair gene mutation	Consider
	Mismatch repair genes to inform response to anti-PD-1 therapy	Consider
Nonmetastatic PCa	*BRCA2* to inform active surveillance	Recommend
	ATM to inform active surveillance	Consider
Men without PCa to inform early detection	Referral to specialty PCa high-risk clinics and/or early detection trials	Recommend
	BRCA2 for early PCa detection starting at 40 years of age or 10 years before youngest PCa diagnosis in family	Recommend
	BRCA1, *HOXB13*, *ATM*, and mismatch repair genes for early PCa detection starting at 40 years of age or 10 years before youngest PCa diagnosis in family	Consider

Shading key: orange for consider, green for recommend.

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EDITORIAL COMMENT

The authors address a "sea change" in PCa management, reviewing the current status of germ line testing. In the past, an increased risk of PCa based on FH was known. This was confined to questions about first- and second-generation relatives with PCa and was a way to raise awareness for early screening. Today, germline testing can be used to identify potentially lethal PCa and to better risk stratify patients. Now germline testing has the potential to impact not only screening but also prognosis and treatment. The knowledge that these genetic alterations impacting individuals who harbor these commonly mutated PCa germ line genes have increased risk for other tumors including breast, pancreatic, ovarian, melanoma and Lynch syndrome-related gastro-intestinal tumors has implications for both broadening our FH questions and for downstream consequences (cascade effects).

This Update includes important information on "who to test." Certainly, testing should be offered to those with localized disease and a strong FH of PCa or related malignancies, or with intraductal/cribriform histology. Testing should also be considered in men with metastatic PCa where 10% may harbor germline mutations, and in men with castration-resistant prostate cancer (CRPC) where the incidence is 25%. Even more impactful is the discovery of druggable targets that are now becoming available in the new era of precision-based medicine. Currently, there are 2 Food and Drug Administration approved PARP inhibitors for the treatment of men with germline or somatic BRCA1/2 alterations or other DNA repair pathway mutated genes and metastatic CRPC as second line therapy.

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1. The type of genes most frequently mutated in the germline of prostate cancer patients are genes that are associated with
   a. cell cycle regulation
   b. DNA repair
   c. apoptosis
   d. immunity

2. Germline testing is recommended for
   a. *APC* in primary prostate cancer
   b. *BRCA2* in metastatic prostate cancer
   c. *AR* in tumors with intraductal histology
   d. *CCND1* in men with a family history of cancer

3. A potential barrier to widespread use of germline testing in prostate cancer is
   a. difficulty in extracting DNA samples
   b. lack of choice in testing assays
   c. lack of genetic counselors
   d. cost

4. The patient who best meets the criteria for germline genetic testing is a 62-year-old man with newly diagnosed
   a. very low risk PCa, with no family history of any cancer
   b. low risk PCa, with a family history of breast cancer in his mother and melanoma in his father
   c. intermediate risk PCa, with a family history of breast cancer in a sister and pancreatic cancer in a brother
   d. metastatic PCa and no family history of PCa or other malignancies

5. Genomic testing focuses on a specimen from the tumor while germline genetic testing utilizes a specimen from
   a. the tumor
   b. a blood draw
   c. a buccal swab
   d. either a blood draw or buccal swab