

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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When to Use Germline Genetic Testing in Prostate Cancer



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H&O What germline DNA repair gene mutations play a role in prostate cancer?

VG Many DNA repair genes play a role in hereditary prostate cancer. These include *BRCA2*, *BRCA1*, *ATM*, and the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Furthermore, *HOXB13* is important in hereditary prostate cancer. This is not a DNA repair gene, but it is associated with risk for prostate cancer.

H&O How common are these mutations, and what is their effect on prostate cancer risk and phenotype?

VG Depending on the study, germline mutations in DNA repair genes are found in 11% to 15% of men with metastatic prostate cancer and 5% to 7% of men with localized prostate cancer. One of the highest risks for prostate cancer is seen in men with mutations in the *HOXB13* gene; these are associated with a lifetime risk for prostate cancer that can be up to 8 to 10 times that of the general population. Mutations in *HOXB13* are also associated with an early onset of prostate cancer.

Mutations in *BRCA2* are associated with a risk for prostate cancer that can be 3- to 4-fold that of the general male population; they are also associated with more aggressive forms of prostate cancer, more advanced disease at diagnosis, and poorer outcomes. The risk for prostate cancer is also elevated with *BRCA1* mutations but is less than with *BRCA2* mutations. Men who have mutations in *BRCA1* or *BRCA2* are also at elevated risk for male breast cancer, pancreatic cancer, and melanoma, and women with these mutations are at an elevated risk for female

breast cancer, ovarian cancer, pancreatic cancer, and melanoma. These elevated risks are important to consider in terms of the patient's cancer risk, as well as the risk among relatives.

Mutations in DNA mismatch repair genes are associated with Lynch syndrome. People with Lynch syndrome are at elevated risk for colorectal cancer, prostate cancer, pancreatic cancer, urinary tract cancer, and specific skin cancers, as well as ovarian and uterine cancer in women.

H&O What are the cancer screening recommendations for men with germline mutations?

VG The National Comprehensive Cancer Network (NCCN) recommends that men who have a *BRCA2* mutation start annual prostate cancer screening beginning at age 40 years, based on results from the IMPACT trial. Screening may need to be repeated even more frequently if prostate-specific antigen (PSA) testing reveals elevated age-specific PSA levels. The recommendation for men with mutations in *BRCA1* is to consider screening starting at age 40 years.

The NCCN guidelines do not yet address the question of prostate cancer screening in men with mutations in *ATM* or *HOXB13*. The National Cancer Institute is conducting an important study of prostate cancer screening (NCT03805919) in men who have a host of various genetic mutations, including mutations in *BRCA1*, *BRCA2*, *ATM*, and *HOXB13*. These men are undergoing magnetic resonance imaging in addition to routine clinical tests to determine the optimal screening strategies for them.

H&O What are the goals of germline genetic testing?

VG The goals are evolving over time. The first goal is to use germline genetic testing for precision medicine indications; this use is rapidly rising in importance. For example, if the disease of a man with castration-resistant metastatic prostate cancer has progressed during initial lines of therapy and he has a *BRCA2* mutation, he could receive treatment with a poly(ADP-ribose) polymerase (PARP) inhibitor. The US Food and Drug Administration has approved 2 PARP inhibitors, olaparib (Lynparza, AstraZeneca) and rucaparib (Rubraca, Clovis Oncology), for men with castration-resistant metastatic prostate cancer and *BRCA1* or *BRCA2* mutations after progression during initial lines of therapy. Olaparib is also approved for men who carry additional DNA repair mutations. The results of germline genetic testing can help us determine the best therapeutic options or clinical trial options for a particular patient. Multiple trials are looking at the use of germline genetic testing in advanced prostate cancer, and trials are also beginning to look at this testing in earlier-stage prostate cancer. Early data published in the early-stage setting by Carter and colleagues reported especially increased rates of biopsy upgrades among men on active surveillance who carried *BRCA2* mutations. These data await confirmation and a delineation of practice considerations.

A second goal of germline genetic testing in prostate cancer is to determine whether a man has a hereditary cancer syndrome, which may point to an inherited predisposition to cancer among both male and female relatives. A third goal of germline genetic testing is to guide screening strategies.

H&O Who should receive germline genetic testing?

VG Men with prostate cancer should be offered germline testing any time that the results of testing could have therapeutic implications. Germline testing should be considered for men with advanced or metastatic prostate cancer because the rates of germline mutations are higher in these individuals, and germline testing should also be considered for patients with intraductal or cribriform carcinoma because they appear to have elevated rates of *BRCA* mutations. Men with high-risk advanced prostate cancer can also be offered germline testing, per the NCCN guidelines. Men in whom cancer is diagnosed at an early age or who have a family history of prostate, breast, ovarian, colorectal, uterine, or pancreatic cancer are also candidates, especially if they have multiple relatives with these cancers or cancers arising at a young age,

or relatives who have died of these cancers. These factors raise the suspicion for a hereditary cancer syndrome in a family.

The indications for germline testing have expanded significantly, which means that the number of patients who need to see a genetic counselor has exploded.

H&O What specific tests are available, and how do you choose among tests?

VG Multiple commercial laboratories offer genetic testing for prostate cancer. It is important to go with a laboratory that has longstanding clinical experience with genetic testing and can interrogate complex genetic regions, classify variants of uncertain significance, follow up with ordering providers for variant reclassification, and incorporate newer technologies. Companies can package their tests in different ways, so they may offer a guidelines panel that includes half a dozen genes, a tumor-specific panel that includes 15 to 20 genes, or comprehensive panels that include 40 to 100 genes. In prostate cancer, we generally want to test for mutations in *BRCA2*, *BRCA1*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *HOXB13*, *CHEK2*, *PALB2*, and potentially *NBN*. A few companies also offer reflex testing, in which the test starts with a small panel and expands to a larger panel if initial results are negative. Additional considerations for choosing a genetic testing laboratory are the patient's insurance coverage and the range of services and testing provided. For example, not every company provides RNA testing, which is emerging as a useful way to determine the functionality of variants of uncertain significance that may affect splicing or are intronic.

Genetic testing should also be informed by the family history, so testing for additional relevant genes should be ordered if a patient with prostate cancer has a family history of other types of cancer.

H&O When should testing be conducted?

VG The timing of testing depends on the patient's clinical

scenario. Germline testing can be appropriate at any time for patients who have metastatic prostate cancer. In some cases, we conduct germline testing as soon as the disease becomes metastatic. Even though the information does not affect first-line treatment at this time, one advantage of early testing is that the patient is in better physical condition, which can make it easier for him to get to appointments and meet with a genetic counselor. Other patients are not interested in genetic testing when metastatic disease is first diagnosed and prefer to wait until their disease progresses. It is important to re-approach patients who initially decline genetic testing so as not to miss the opportunity to uncover a hereditary cancer syndrome. Men with early-stage prostate cancer, men without prostate cancer, and prostate cancer survivors can all be approached at any point during their care if they meet the criteria for germline testing.

H&O Should physicians start with somatic tumor testing, or should they start with germline tumor testing?

VG Even though some overlap between somatic testing and germline testing is possible, they are not equivalent, and the best approach is to conduct them concurrently for men who meet genetic testing criteria. Even if the results of tumor testing are negative, the patient may still carry a germline mutation, so germline testing should still be considered if the patient meets the criteria.

H&O Who should make the decision to order germline testing?

VG The traditional model has been for physicians to identify and refer patients to genetic counselors for genetic counseling and the ordering of genetic testing. It is recognized that the indications for germline testing have expanded significantly, however, which means that the number of patients who need to see a genetic counselor has exploded. The relative shortage of genetic counselors has become an issue in practice, so urologists, oncologists, and other physicians are having to think about ordering their own genetic testing.

I recommend that physicians who are thinking about initiating their own genetic testing work to build a collaborative relationship with a genetic counseling service. Physicians should discuss with the genetic counselor the situations in which they can order testing, and which tests are the most appropriate to order. Just as important is to set up a referral process so that once the results come back, physicians know whether they can deliver the information themselves and whether genetic counseling is required. This is an evolving field, and models must be adapted as

we go forward to handle the volume of patients who need testing.

H&O Is there anything that you would like to add?

VG It is very important to think about diverse populations when we are considering genetic testing. We need to pay attention to disparities between awareness of genetic testing and access to genetic services across various populations. How can we provide equitable access to genetic counseling and testing and ensure that we are not missing populations that require this type of technology? We also need to deliver genetic information at a level that is tailored to the patient, with attention to medical literacy and numeracy. A lot of work remains to be done regarding health equity and the delivery of genetic services.

At Jefferson, we are conducting multiple studies funded by grants from the US Department of Defense (DOD) that are focused on studying peer-based ways to increase awareness of genetic testing, engagement in genetic counseling, and use of testing among African American men. Peer-based approaches and other approaches are needed to reach and engage diverse populations in this field.

H&O Are there opportunities for research collaboration and education regarding prostate cancer genetics?

VG There are multiple opportunities for collaboration, including the PROGRESS Registry, the ENGAGEMENT Study Virtual Genetics Board, the PRECISION Registry, and the TARGET Study. I am the principal investigator for PROGRESS and ENGAGEMENT, both of which are funded by the DOD Idea Development Award, and the lead principal investigator for PRECISION and TARGET, both of which are funded by the Prostate Cancer Foundation Challenge Award.

PROGRESS (www.progressregistry.com) is a national, patient-driven registry for any male who has undergone or is currently undergoing genetic testing for prostate cancer. The goal of the registry is to collect information on men's experience with genetic counseling and genetic testing to help inform the development of resources to help men and their families with this process. Any male who has undergone genetic testing for prostate cancer can be referred to the website to participate. Participants receive \$50 for the completion of surveys, and receive a periodic newsletter to keep them informed of the work from the registry and new findings in the field.

The ENGAGEMENT Study Virtual Genetics Board (www.prostategenetics.com/engagement) provides a novel

opportunity for health care providers, genetic service providers, trainees, advocacy members, and scientists to engage in case-based learning about the issues surrounding genetic testing, genetic counseling, genetic-based management, and the implications of hereditary cancer for genetic evaluation of prostate cancer. Participants can join live or listen to current and prior recordings of case discussions. The expert panel includes broad expertise in medical oncology, cancer genetics, radiation oncology, urology, genetic counseling, and molecular oncology. Continuing medical education credit is available for those who join live.

We want to improve our understanding of factors that modify the responses to PARP inhibitors, with the goal of improving patient benefit from these agents. The PRECISION Registry is an international registry of clinical and genomic data from men with prostate cancer treated with PARP inhibitors. It is a collaboration between Thomas Jefferson University, Duke University, and the University of British Columbia, and will include data from patients in clinical trials, registries, academic centers, molecular laboratories, and clinical sites. Physicians who are interested in collaborating can contact the study team at www.precision-registry.com.

Given that prostate cancer genetic testing has expanded, there is a need to study alternate delivery of pretest genetic education to expand access to informed consent for genetic testing. The TARGET Study is a multi-institutional randomized trial of a pretest genetic education web tool vs genetic counseling. The study will be open until the end of 2022, and is available to men with prostate cancer who meet genetic testing criteria and who reside in Pennsylvania, New Jersey, New York, or Washington. Physicians who wish to refer patients to the study can contact the study team at <https://www.prostategenetics.com/target>.

Disclosure

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Suggested Readings

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