
How I Do It: Genetic counseling and genetic testing for inherited prostate cancer

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GIRI VN, GROSS L, GOMELLA LG, HYATT C.
How I Do It: Genetic counseling and genetic testing for inherited prostate cancer. *Can J Urol* 2016;23(2): 8247-8253.

Prostate cancer has a substantial heritable component, which is often under-appreciated in the urologic community. Inherited prostate cancer which may account for up to 10% of cases has been associated with genetic mutations which are also linked with other hereditary cancer syndromes. Therefore, family history indicating inherited prostate cancer predisposition may extend beyond prostate cancer to include other cancers such as breast, ovarian and others.

Genetic counseling and genetic testing guidelines for prostate cancer are slowly emerging, which emphasizes the need for urologists and other providers involved in the care of prostate cancer patients to consider referring appropriate prostate cancer patients for genetic counseling. Here we will highlight the key elements involved in prostate cancer risk assessment, current knowledge of genetic contribution to prostate cancer, and factors for urologists and other providers to consider when referring prostate cancer patients for genetic counseling.

Key Words: prostate cancer, genetic testing, cancer risk, genetic counseling

Introduction

Genetic testing for cancer predisposition refers to evaluation of candidate genes based upon the patient's personal cancer features, medical history, and family cancer history. The purpose of genetic testing is to determine if a germline (inherited) mutation can be identified to inform the patient about potential cancer management and risks for additional cancers based on the gene. Furthermore, germline mutations can be

transmitted to offspring and can be identified in any blood relative depending on the inheritance pattern, and therefore can have implications for cancer screening and management for family members.¹ This approach to "genetic testing" is in contrast with tumor "genomic" testing where tumor samples are assessed for marker patterns to inform disease aggressiveness and prognosis in order to guide cancer treatment. In addition, as tumor sequencing is rapidly being incorporated into oncology, this may also be confused with classic "genetic testing". In tumor or somatic massively parallel sequencing, the patient's tumor and normal tissues are sequenced for mutations in multiple genes or genomic regions to help determine the best targeted therapy. It is therefore crucial for clinicians to be aware of the different approaches to genetic and genomic testing, and to help patients understand the differences.

Accepted for publication March 2016

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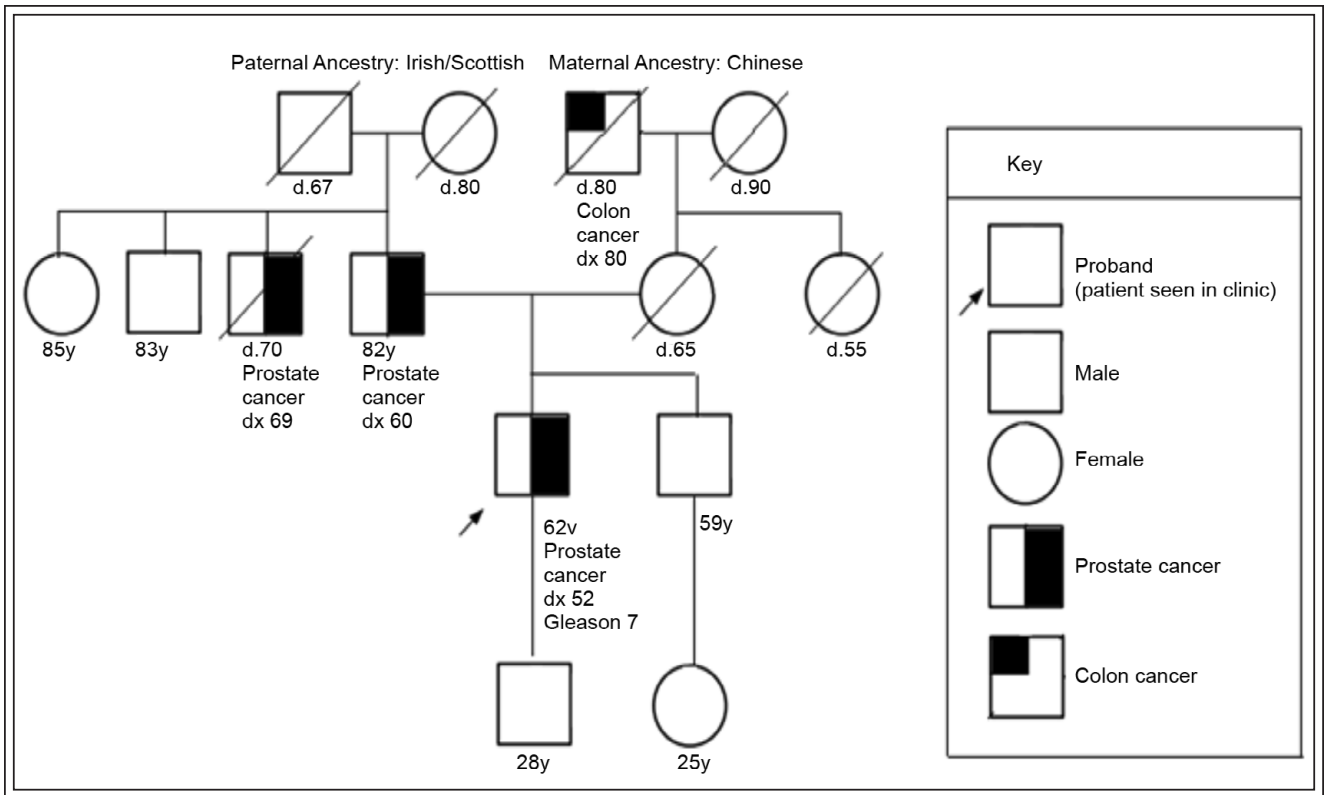


Figure 1a. Hereditary prostate cancer showing the proband (with arrow) with prostate cancer diagnosed at age 52, patient’s father diagnosed with prostate cancer at age 60, and paternal uncle with prostate cancer at age 69.

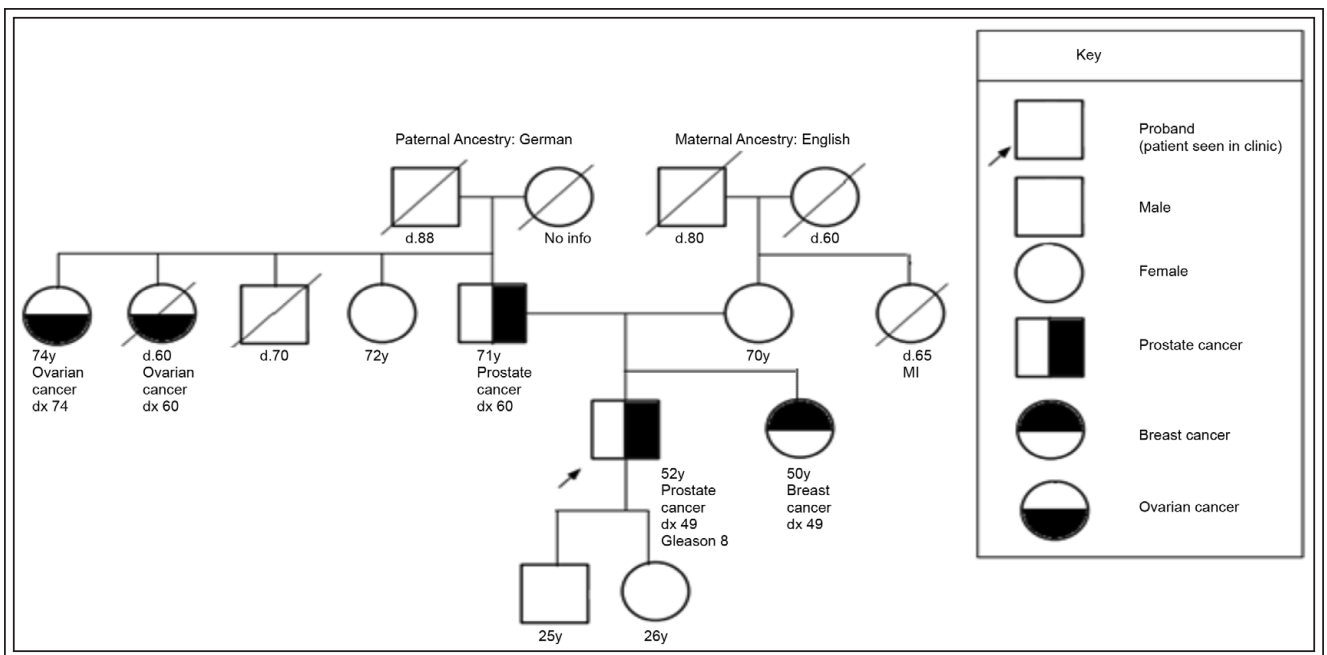


Figure 1b. Hereditary breast and ovarian cancer syndrome showing the proband (with arrow) with prostate cancer diagnosed at 49, patient’s sister with breast cancer diagnosed at 49, patient’s father with prostate cancer diagnosed at 60, and two paternal aunts with ovarian cancer.

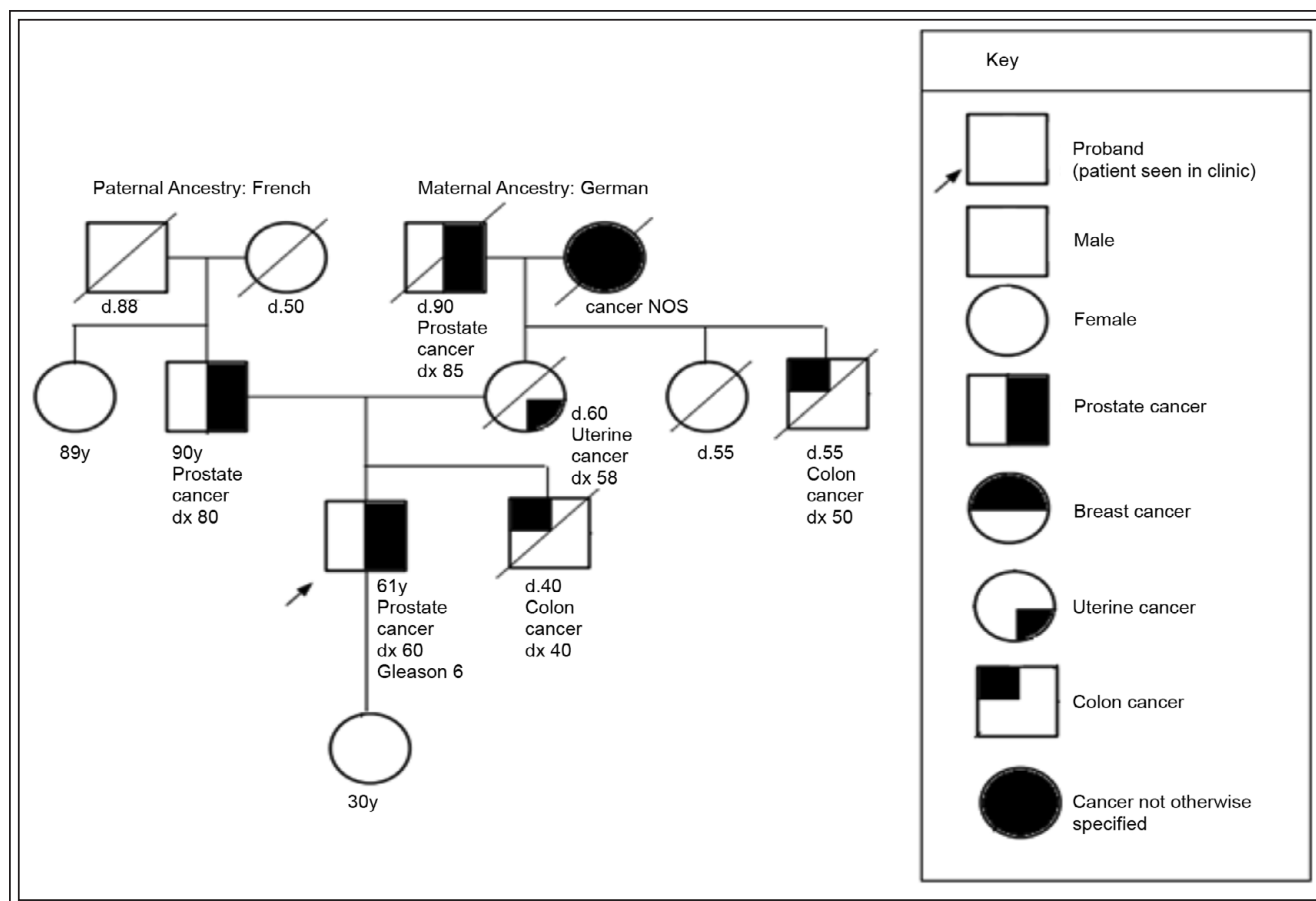


Figure 1c. Suspected Lynch syndrome pedigree showing the proband (with arrow) with prostate cancer diagnosed at 60, brother with colon cancer diagnosed at 40, mother with uterine cancer diagnosed at 58, and maternal uncle with colon cancer diagnosed at 50.

Prostate cancer is one of the most highly heritable cancers, with an overall estimated inherited component of ~40%-50%.^{2,3} Approximately 5%-10% of inherited prostate cancers are accounted for by rare mutations in highly penetrant genes. Family studies and next-generation sequencing approaches have identified subsets of prostate cancer associated with germline mutations in *BRCA1*, *BRCA2*, and *HOXB13*.⁴ *BRCA1* and *BRCA2* mutations have been associated with a strong family history of breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, and/or melanoma as part of hereditary breast and ovarian cancer syndrome (HBOC).⁵ Furthermore, *BRCA2* mutations have been associated with a more aggressive prostate cancer phenotype.^{6,7} A recurrent mutation in *HOXB13* has been associated with an approximate 2 to 8-fold increase in risk for hereditary prostate cancer (HPC), the features of which include generational prostate cancer, multiple first-degree relatives with prostate cancer, or prostate cancer diagnosed at age ≤ 55 years.^{4,8-10} Furthermore,

molecular studies of prostate cancer have estimated prostate cancer risk of over 3-fold in DNA mismatch repair gene mutation carriers associated with Lynch syndrome, which is characterized by a strong family history of multiple cancers including colorectal cancer, ovarian cancer, uterine cancer, gastric cancer, and/or sebaceous adenocarcinoma.¹¹ Figure 1a, 1b and 1c highlights examples of familial cancer features indicative of HBOC, HPC, and Lynch syndrome where the presenting patient (proband) is a patient with prostate cancer. Though clinical genetic testing is available for the genes linked with HBOC, HPC, and Lynch syndrome, guidelines supporting genetic testing for prostate cancer probands are limited and are emerging secondarily from other cancer syndromes (such as hereditary breast and ovarian cancer guidelines) which poses challenges for insurance coverage and subsequent implementation of genetic testing. However, when inherited prostate cancer is suspected, referral to genetic counseling is critical to assess cancer risk, provide patients with

TABLE 1. Spectrum of cancer risks for genes associated with prostate cancer predisposition

	Prostate	Breast	Ovarian	Pancreatic	Melanoma	Colon	Gastric/ small bowel	Uterine	Sebaceous carcinoma
<i>BRCA1</i> and <i>BRCA2</i>	x	x	x	x	x				
DNA mismatch repair genes*	x		x			x	x	x	x
<i>HOXB13</i>	x								

*Studies describe higher rates of prostate cancer in Lynch syndrome families. Emerging data implicate DNA mismatch repair genes in prostate cancer predisposition, though definitive studies are warranted.

information to help determine if testing is right for them and the family, and to streamline the testing process.

A genetic counselor is a healthcare professional with specialized training in medical genetics and counseling for genetic testing. The genetic counselor is central to the process of genetic evaluation to inform patients about the benefits and limitations of genetic testing, implications of cancer risks for patients and their families, and further management based upon existing practice guidelines. Genetic counselors also coordinate genetic testing with commercial laboratories and meet with patients after test results are available (disclosure visit) to interpret test findings and place findings in the context of the individual's family cancer history. Therefore, referral to genetic counseling is crucial for prostate cancer genetic testing to address cancer risk implications for the patient and their family. Table 1 highlights the cancer risks associated with mutations in the genes implicated in prostate cancer inheritance. As can be seen in Table 1, a mutation in a given gene can predispose the proband to the cancer in question (in this case prostate cancer) but may also predispose to additional cancers which were unanticipated by the patient. Depending on the cancers, heightened screening or additional screening may be needed that were not expected for the patient presenting for genetic testing. Furthermore, genetic test results may be inconclusive. A negative genetic test result may not necessarily rule out a familial mutation if there was not a mutation identified in the family. Without a positive test in a family member, the negative result in the proband (individual presenting for genetic counseling) would be interpreted as indeterminate or inconclusive. An additional finding that can be reported to the patient is variant of uncertain significance (VUS).

These variants do not meet all laboratory criteria to be classified as pathogenic or benign, and are reported to patients as uncertain significance. These variants are typically followed to gather more evidence and may be reclassified to pathogenic or polymorphism. However, VUSs can cause patients anxiety or be misinterpreted by clinicians and patients as a mutation, leading to unnecessary recommendations for cancer screening or risk reduction measures. Therefore, an experienced genetic counselor or genetics professional is crucial to educate and assist patients about potential test results and implications for the patient and their family to make an informed decision about genetic testing for inherited cancer risk assessment.

Method

Institutional priority to address field challenges

Advancing the field of genetic testing for prostate cancer has become a commitment at our institution. As such, a genitourinary (GU) genetics clinic was started with a dedicated focus in evaluating patients with or at-risk for GU cancers for inherited cancer predisposition with formal genetic counseling and genetic testing. For maximal point of contact with patients and urologic providers, our institution has implemented the GU genetics clinic alongside of the existing GU Multidisciplinary clinic – a dynamic multispecialty clinic where patients with prostate cancer can have consultations from urologic oncology, radiation oncology, and medical oncology regarding their prostate cancer management.¹² Appropriate patients presenting to the multidisciplinary clinic are offered an opportunity to undergo genetic consultation to round out their assessment.

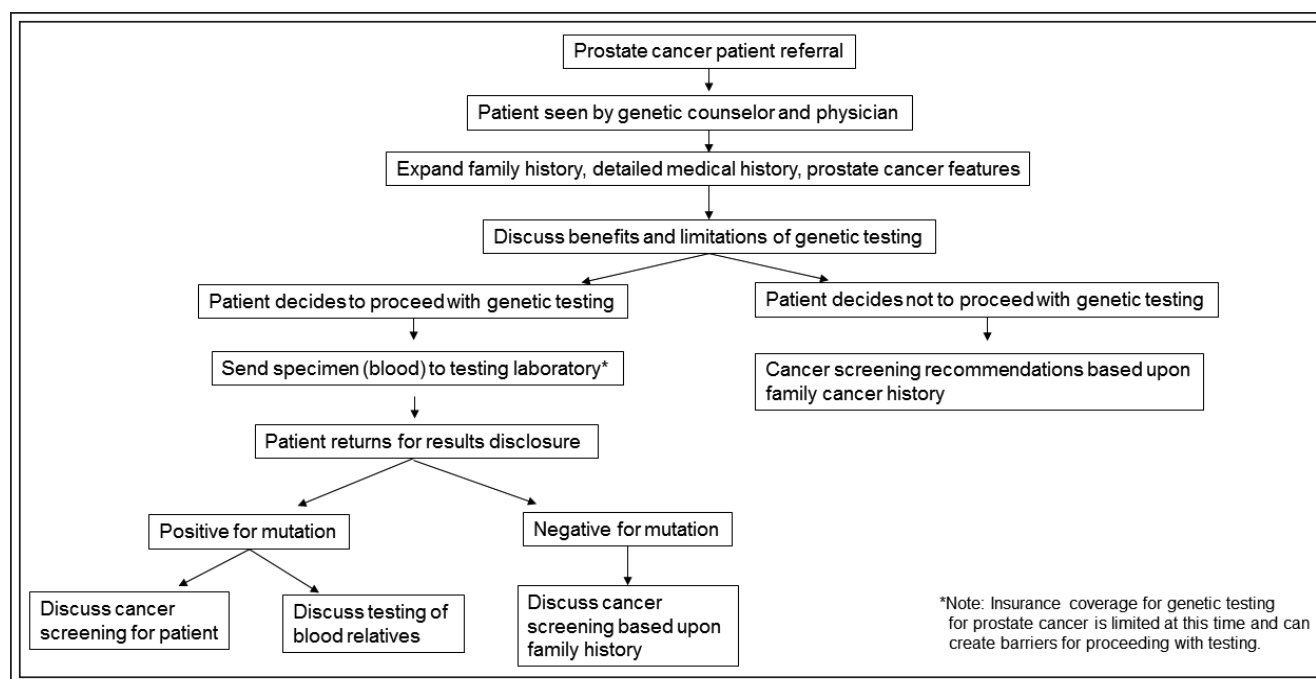


Figure 2. Proposed clinical flow of genetic evaluation for inherit prostate cancer.

At this time, insurance coverage for genetic testing of prostate cancer is challenging which limits the ability of prostate cancer patients to have genetic testing covered. One reason is that national guidelines are very focused regarding which prostate cancer patients warrant genetic evaluation. Patients meeting criteria may have genetic testing covered by some insurance plans. Multiple commercial laboratories are options for patients to perform genetic testing, including Myriad Genetics, Inc., Ambry Genetics, GeneDx, and Invitae. However many patients fall outside of genetic evaluation guidelines and cannot have testing covered by insurance, though the suspicion for inherited predisposition remains. Therefore, clinical genetic investigational studies are critical to expand the understanding of the genetic spectrum of prostate cancer predisposition and gain insights into clinical application. Such a clinical genetic testing study is available to prostate cancer patients meeting eligibility criteria at our institution. Figure 2 shows the clinical flow for genetic evaluation of inherited prostate cancer at our institution.

Referral criteria for providers

Referral criteria for prostate cancer patients for genetic evaluation at our institution have been developed after consensus by urologic oncology, medical oncology, and radiation oncology providers. These criteria take a broad approach in order to incorporate the potential spectrum of patients who may have

suspected inherited prostate cancer. Referral criteria for genetic evaluation include any of the following: 1) prostate cancer diagnosis at age ≤ 65 , 2) Gleason score > 7 and family history of cancers related to HBOC (cancers of the breast, ovary, pancreas, or prostate), or 3) family history of cancers relevant to HBOC, HPC, or Lynch syndrome particularly in first-degree or second-degree relatives given the implication of prostate cancer in these syndromes (includes cancers of the breast, ovary, pancreas, prostate, colon, uterus, upper tract urothelial cancer, small bowel). Table 2

TABLE 2. Referral criteria for prostate cancer patients for genetic evaluation

Referral criteria	References
Age at prostate cancer diagnosis ≤ 65 years	13
Gleason score > 7 and family history of cancers related to HBOC	5
Family history of cancers relevant to HBOC, HPC, or Lynch syndrome particularly in first-degree or second-degree relatives given the implication of prostate cancer in these syndromes	5, 8-11

HBOC = hereditary breast and ovarian cancer syndrome
HPC = hereditary prostate cancer

summarizes these criteria along with evidence or guidelines supporting their development. Again these referral criteria are broad in order to capture the subset of individuals who may benefit from genetic evaluation and to enhance feasibility of referrals from busy urologic practices.

Genetic counseling

Patients are scheduled for genetic evaluation, which entails meeting with the genetic counselor and physician with expertise in cancer genetics. The genetic counselor gathers detailed family cancer history information regarding maternal and paternal sides of the family as well as ancestry in order to gauge suspicion for inherited predisposition to prostate cancer and other hereditary cancer syndromes. The genetic counselor also discusses basic genetics, cancer inheritance patterns, information to be gained from genetic testing, limitations or uncertainties from test results, additional cancer risks for patients based on mutations in specific genes, and implications for the patient and their family. Additional discussion includes any insurance barriers to having testing covered, payment plans offered by testing labs, and genetic discrimination laws (what is covered and not covered). The physician expands upon any area of genetics and familial implications, discusses potential medical management based upon test results, and open studies for which the patient may be eligible.

Genetic testing and disclosure

At this time, clinical genetic testing not associated with a clinical research study is limited to testing for mutations in *BRCA1* and *BRCA2* as supported by current NCCN practice guidelines (NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian version 2.2015). The specific NCCN genetic evaluation criteria include personal history of prostate cancer (Gleason ≥ 7) at any age with ≥ 1 close blood relative with breast (≤ 50 years) and/or invasive ovarian and/or pancreatic or prostate cancer (Gleason score ≥ 7) at any age. These criteria highlight the importance of obtaining a detailed and thorough family cancer history on the maternal and paternal sides of the family for an individual presenting for prostate cancer risk evaluation. Occasionally, it may be recommended that a blood relative of the prostate cancer patient is the optimal person to test in the family. For example, if the patient has a sister with young age at breast cancer diagnosis, her genetic test result may be more informative regarding mutation status in the family and may have a greater chance of insurance coverage. Once genetic test results are available, the patient returns for a results disclosure visit with the genetic counselor and physician to review the test results and interpretation of findings.

Genetically-based management

Positive for mutation

If a *BRCA1* or *BRCA2* mutation is identified in the proband, the disclosure session is focused on discussion of the role of that mutation in prostate cancer predisposition and the risk for other cancers implicated in the *BRCA*-spectrum.^{5,14} These additional cancers include cancers of the breast, ovary, pancreas, and melanoma. The discussion is primarily focused on additional cancer screening that may be considered by the prostate cancer proband due to the elevated cancer risks, such as male breast cancer screening, pancreatic cancer screening, and skin cancer screening. NCCN guidelines recommend that male *BRCA* mutation carriers have a clinical breast exam every 12 months starting at age 35, and be taught how to perform their own breast exam also starting at age 35.⁵ There are currently no standard guidelines for pancreatic cancer screening, and therefore patients with *BRCA* mutations are referred to gastroenterology to discuss the pros and cons of pancreatic cancer screening approaches. *BRCA* mutation carriers are also referred to dermatology for focused skin exam of moles or suspicious skin findings and to continue on yearly dermatologic visits. The role of *BRCA* mutations in prostate cancer management is emerging. Recent data demonstrate superior response of prostate cancer patients with metastatic, castrate-resistant disease and a *BRCA* mutation to PARP inhibition.¹⁵ Precision medicine efforts are expected to significantly advance the translational impact of genetic data in the management of localized and advanced prostate cancer.

Another important focus of discussion for *BRCA* mutation carriers is genetic testing for blood relatives. Unaffected male relatives (sons, brothers, nephews) could undergo site-specific genetic testing for the mutation identified in the proband to determine if they have inherited the mutation. For unaffected male relatives with a *BRCA* mutation identified, one issue to discuss is how this impacts prostate cancer screening strategies. Current NCCN guidelines recommend prostate cancer screening starting at age 40 for *BRCA2* mutation carriers, and to consider screening starting at age 40 for *BRCA1* mutation carriers.⁵ Additional data from the ongoing IMPACT study (an international study investigating the role of *BRCA1*, *BRCA2* and Lynch syndrome gene alterations in prostate cancer screening outcomes) may inform prostate cancer screening guidelines by mutation status.¹⁶

Negative for mutation

For patients not found to carry a *BRCA* mutation and no known mutation in the family, the result is interpreted as "inconclusive" since there may be additional genetic factors contributing to inherited prostate cancer beyond

what was tested. The disclosure session is primarily focused on cancer screening recommendations for the prostate cancer patient based upon family history. For example, if there is a strong family history of colon cancer, the patient is recommended to consult with a gastroenterologist for more frequent colonoscopies. The disclosure session also encompasses cancer screening for blood relatives. Unaffected first-degree male relatives (particularly sons and brothers) are recommended to have a discussion of PSA-based prostate cancer screening starting at 40 based upon family history of prostate cancer.¹⁷ Additional cancer screening recommendations for relatives (such as breast cancer or colon cancer screening) are based upon reported family cancer history, such as age to begin screening and frequency of screening, as per existing guidelines.^{5,18}

Variant of uncertain significance (VUS)

Genetic test reports can also include variants of uncertain significance in the genes tested. Current consensus in the field is that management recommendations do not change based upon identifying a VUS. The genetic testing laboratory with experience in clinical testing will follow these variants over time to gather more evidence to determine if a reclassification is possible. Over time, many of these VUSs are reclassified to pathogenic/likely pathogenic (disease-associated) or benign. The laboratories inform ordering doctors when a variant is reclassified so that patients can be notified of the potential need to return for additional disclosure discussions. Therefore, it is essential to know the variant reclassification policy of a commercial genetic testing laboratory, as well as follow up policy with ordering physicians and patients.

Conclusion

Though multiple genes are identified to contribute to prostate cancer inheritance, guidelines are needed regarding how best to incorporate genetic testing into clinical practice. Our approach of offering genetic counseling and focused clinical genetic testing opens the door to addressing inherited cancer risk concerns for prostate cancer patients and their families. Clinical genetic testing studies, such as at our institution, are beginning to identify a broader range of genetic contribution to prostate cancer risk, which is expected to inform interpretation of inherited predisposition and cancer risk management. All of these efforts point to the need to develop the field of genetic testing for inherited prostate cancer in order to provide more comprehensive and informative genetic testing for prostate cancer patients and their families to personalize cancer risk reduction, screening, and treatment approaches. □

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