Genetic Counseling for Men with Prostate Cancer

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KEYWORDS

• Genetic counseling • Prostate cancer • Genetic testing • Genetic counselor
• Hereditary prostate cancer

KEY POINTS

- Genetic testing is an important aspect of patient care in urology clinics for men with prostate cancer and/or patients with a family history of prostate cancer.
- Genetic counseling is an important component of genetic testing for prostate cancer.
- It is important to provide informed consent before genetic testing to allow the patient to make an autonomous decision regarding genetics testing.
- To help ensure informed consent before undergoing genetic testing for inherited risk of prostate cancer, it is important for the patients and/or their families to have genetic counseling.

INTRODUCTION TO GENETIC COUNSELING

As somatic and germline genetic testing continues to play an increasing role in oncology precision medicine, the need for genetic counseling by informed providers increases.[1] Germline genetic testing has become particularly important for patients with prostate cancer because of the possible therapeutic implications and high rate of detectable germline mutations. Germline mutation positivity may affect men's future cancer risk and treatment decisions, and may also have implications for their family members. This article reviews genetic counseling and how it relates to genetic testing in hereditary prostate cancer.

Overview of Genetic Counseling

In order to understand genetic counseling, it is important to have some historical perspective. As genetics knowledge made its way from the bench to clinical practice, genetic counseling emerged to meet a need for patient education and psychological support in what was the brave new world of twentieth century genetics. It was in 1947 that the geneticist Dr Sheldon Clark Reed was the first to use the term genetic counseling.[2] In 1947, Dr Reed was chosen to be the Director of the Dight Institute for Human Genetics at the University of Minnesota. This appointment was during a time when medical geneticists were attempting to separate themselves from the eugenics movement. During his time at the Dight Institute, he learned about not only the medical implications of genetics but also the psychological aspects. He was the first to suggest the term genetic counseling to describe the process of providing medical information and psychological support to patients.[2] In the 1970s, genetic counseling emerged as a bona fide profession to help meet the needs of people considering genetic testing so they could obtain the correct information necessary to understand what genetic testing was and how it could affect them and their families, and to understand and manage psychologically their genetic test results.

Although genetic counseling initially existed in the reproductive and pediatric specialties, it has greatly expanded over time to meet the

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needs of new medical advances and the patients that opt to use them. Specifically, there has been an expansion in the role of genetic counseling in adult-onset diseases and specifically in oncology. For genetic counselors, this means an evolving role in patient care, including providing information related to risk assessment for complex disorders, chemoprevention, targeted drug therapy, cancer screenings, and prophylactic surgery.[3]

Definition of genetic counseling

The National Society of Genetic Counseling (NSGC) definition of genetic counseling states that "genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease."[4] This process integrates:

1. Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
2. Education about inheritance, testing, management, prevention, resources, and research.
3. Counseling to promote informed choices and adaptation to the risk or condition.

Most genetic counseling services are now provided by a board-certified genetic counselor that has completed, at minimum, a master's-level education program related to genetics and/or genetic counseling. Other qualified genetic counseling professionals include physicians and PhDs with advanced training in genetic counseling, and master's-prepared advanced practice nurses with advanced training and board certification in genetics.[3]

Along with collecting thorough personal and family history, a genetic counseling professional provides accurate, current information including the risks, benefits, and limitations of genetic testing, so that individuals can make informed decisions about whether to proceed with genetic testing. Also in the realm of the genetics professional is to help individuals to psychologically and operationally managing their genetic test results, whether positive or negative. Genetic counselors facilitate referrals to clinicians that specialize in certain high-risk aspects of individualized patient care. Thorough written summaries including current medical management and risk-reduction options for the patients and their family members are provided to the patients and their participating clinicians by the genetic counselor.

When positive genetic test results occur, the genetics counselor can facilitate cascade genetic testing in the family, or help the family find a qualified genetics provider in their geographic area.

At its core, genetic counseling strives to facilitate a trusting, collaborative relationship between counselor and patient that affords the patients unconditional positive regard and the control to make their own choices about genetic testing.[3] After participating in a genetic counseling session, some patients opt to go forward with testing, and others return later after they have had some time to digest what was discussed during counseling. Some need to first get their insurance situation settled. Others may opt to never proceed with genetic testing. The key element lies with the informed decision making and understanding of the patient. Patients should be in control of their own decisions, and confidently have been provided the correct understandable information, and nonjudgmental psychological support to reach those decisions.[3]

CANCER GENETIC COUNSELING SESSION

Traditionally, a genetic counseling session involves a pretest counseling session and then a posttest counseling session, if genetic testing was ordered. The components of pretest and posttest genetic counseling are outlined next.

Pretest genetic counseling

Pretest genetic counseling is done as a part of the cancer risk assessment before ordering genetic testing in order to facilitate informed decision making (see **Table 2**). This process should include evaluating the patient's needs; obtaining a comprehensive family, medical, and surgical history; creating a differential diagnosis; identifying the best relative to pursue genetic testing; educating about the basics of genetics and inheritance; discussing which genetic testing would be best and the possible types of genetic test results; and addressing privacy and psychosocial issues.[5,6] The genetic counselor also discusses insurance coverage and cost of genetic testing with the patient during this process. Pretest counseling has been shown to reduce negative outcomes such as psychosocial effects, misunderstanding of genetic test results, inappropriate medical management, and unnecessary genetic testing.[7,8]

At the beginning of a genetic counseling session, the genetic counselor sets an outline for the session together with the patient. Through contracting, the genetic counselor elicits the patient's goals for the session, often beginning by asking why the patient has come for genetic counseling.[3] This approach helps to establish rapport, identify

specific questions and psychosocial concerns, and elicit the patient's expectations, thereby allowing the genetic counselor to tailor the session to meet the patient's goals.[3,9] Through this process, the genetic counselor and patient establish an agreed-on plan for the session.[3]

Once contracting is completed, a medical and family history are obtained, followed by a discussion of the necessary elements for optimal informed consent.[6,9] An essential part of pretest genetic counseling is discussing the purpose, benefits, and limitations of genetic testing. This process includes discussion of what it would mean to find a germline mutation with regard to implications for the patient and the patient's family. The genetic counselor also helps identify the best relative in the family to pursue genetic testing, because testing is most informative when pursued by a relative who has had a cancer diagnosis. Unaffected individuals can undergo genetic counseling but, in the absence of a known familial mutation, the results are often considered inconclusive. If applicable, testing options, such as a prostate cancer–focused panel compared with a more expanded cancer panel, are also discussed as well as the different types of test results that are possible, including positive, negative, and variant of uncertain significance (VUS).

It is common for individuals to overestimate their personal cancer risks. This possibility has been shown in many cancer genetics studies across various cancer types, including prostate cancer.[3,10,11] Effective genetic counseling does not cause increased risk perception and can result in a decrease in perceived cancer risk.[10,12] Perceived cancer risk has been shown to correlate with whether patients follow through on cancer screening and risk-reduction recommendations as well as psychosocial concerns.[13,14] Therefore, genetic counselors should address any discrepancy between a patient's perceived cancer risk and the actual cancer risk.

Importance of family history and pedigree

Obtaining a thorough family history is an integral part of the cancer genetic counseling session. This history allows genetic counselors to establish a differential diagnosis, perform a risk assessment, and make recommendations for genetic testing and medical management as well as to provide information for family members about genetic counseling, genetic testing, and cancer screening recommendations.[3,7] A comprehensive family history is obtained by creating a 3-generation medical pedigree, which is a visual representation of a patient's family history using standard pedigree nomenclature.[5,15] The genetic counselor asks questions about all first-degree, second-degree, and third-degree relatives regarding cancer diagnoses, including age at diagnosis as well as relevant cancer screening, risk-reducing surgeries, and genetic testing results. In the evaluation of men for inherited prostate cancer risk, it is important to ask targeted family history questions in terms of prostate cancer history, including whether any relatives had metastatic prostate cancer or died of prostate cancer.[6] In addition, it is important to obtain information regarding ethnicity, particularly Ashkenazi Jewish ancestry, and consanguinity. This information is typically obtained during the pretest genetic counseling session before the risk assessment and counseling.[3] Through this process, a genetic counselor may learn about a patient's family and social relationships, which can assist in addressing a patient's psychosocial needs.[3]

The process of obtaining a detailed family history can present several challenges. It can take a significant amount of time to complete a thorough family history with a patient, which can be a limiting factor in many primary care and specialists' offices. Genetic counselors typically spend 60 to 90 minutes on each new patient appointment, allowing for adequate time to take a detailed family history.[5] Limited family history information, such as for patients who are adopted, estranged from their relatives, or have a small family structure, can also present a challenge in cancer genetic counseling. These factors may cause it to seem that there is a low risk for a hereditary cancer syndrome in a family and therefore need to be taken into consideration when analyzing a pedigree.[16] It is common for there to be inaccuracies in the information provided to the genetic counselor by the patient. Therefore, when possible, it is important for family history information to be confirmed with medical records.

The family history is an important tool to determine whether an individual meets criteria for genetic testing, establish a differential diagnosis, and discuss appropriate genetic testing options. Taken together, this information also assists genetic counselors in making referrals to appropriate specialists to further discuss high-risk cancer screenings. Factors that may indicate a hereditary cancer syndrome include many relatives with similar or related cancers, early-onset cancers, individuals with multiple primary or bilateral cancers, and the diagnosis of a rare cancer type.[16] Family history criteria for germline prostate cancer genetic testing include men with 1 first-degree relative or 2 or more male relatives diagnosed with prostate cancer before 60 years of age, who died

of prostate cancer, or who had metastatic prostate cancer, as well as a family history of cancers associated with hereditary breast and ovarian cancer syndrome (HBOCS) or Lynch syndrome.[6] Additional considerations in family history interpretation include variable expressivity, reduced penetrance, and an extensive negative family history.

Posttest genetic counseling

In a posttest genetic counseling appointment, a genetic counselor thoroughly reviews genetic testing results with the patient and discusses cancer risk and associated management guidelines in the context of the patient's personal and family history.[3] At this time, referral to high-risk providers may also be discussed. In order to optimize management options for evaluation and medical care, results should be communicated in a timely manner.

Results of genetic testing do not always provide a clear answer. Most genetic variants are classified using the standards and guidelines established by the American College of Medical Genetics; however, available technology and methodology vary between laboratories.[17] Variants are classified using the following 5 tiers: benign, likely benign, VUS, likely pathogenic, and pathogenic.[18] When these findings are discussed with a patient, they are conveyed as either negative, positive, or uncertain results.

A negative result means that neither a clinically significant variant nor a VUS was detected in the genes that were analyzed.[3] For patients with a known highly penetrant mutation in the family, this can mean that the patient's risk of developing associated cancers is decreased and closer to the risk seen in the general population. These individuals are known as true negatives because they do not carry the pathogenic variant causing the cancer risks in their families. However, most do not have a known familial pathogenic mutation that explains their personal and/or family histories. For these individuals, a thorough risk assessment in the context of a negative test result is discussed. Screening and medical management guidelines discussion should be based on personal and family history. For all patients, it is imperative to discuss the limitations of genetic testing. These limitations can include technological limitations of the laboratory, limitations in genetic knowledge and technology, and not testing the best candidate in the family.

A positive genetic testing result means that a pathogenic or likely pathogenic variant was detected in one of the genes tested. A positive result can be emotional for the patient.[3] It is important to thoroughly discuss associated cancer risks and next steps in a way that the patient understands. Sometimes this can take multiple appointments to ensure that the patient has had time to think through the initial information and is comfortable discussing the next steps. Next steps will depend on what gene the pathogenic or likely pathogenic variant was detected in, and they may include high-risk screening for prostate and other cancer risks depending on the specific gene mutation and notifying family members of their risk. In some cases, this involves surgery for the patient or family members for risk reduction. To identify other family members that may be at risk, testing for an identified pathogenic variant must then extend to relatives in a process known as cascade testing. Cascade testing can identify at risk relatives as well as true-negatives, allowing appropriate family members to undergo high-risk screening.[1,5]

An uncertain result or VUS means that, at the time of interpretation, there was not sufficient evidence to determine whether the variant was positive or negative. Although VUSs are reported to patients in their genetic test results, they usually have no implications for management at the time of reporting.[3] VUSs are followed over time by genetic testing laboratories for evidence in support of pathogenicity and are reclassified as either pathogenic or benign. A 2018 study including more than 1 million genetic test results showed that, in a span of 10 years, 7.7% of VUS results detected in testing were reclassified, of which 91.2% were downgraded from a VUS to benign or likely benign. Although extremely rare, reclassification can also occur in variants previously thought to be pathogenic or benign.[19] Given the eventual reclassification of these variants, all patients that have had genetic testing should keep in contact with their genetics programs or other ordering providers to be aware of any reclassifications. It is also important for the ordering provider to know how the ordering laboratory treats VUSs. Some genetic testing laboratories regularly evaluate VUS results and make ordering providers aware of any future reclassifications, but not every laboratory has this policy in place.

Multigene testing has increased the complexity of the typical results discussion. In particular, understanding of VUS results on cancer risk can be difficult for patients. With multigene panel testing becoming the standard of care, rates of VUS results have increased.[17,20] A research study on 109 men with prostate cancer undergoing genetic testing showed a discordance of reported genetic testing results with actual reported results. This

discordance was specifically true for those with a VUS.[21] This finding highlights the importance of an in-depth discussion of results regardless of the type of result obtained.

Past research has consistently reported no long-term adverse psychological outcomes for the most individuals undergoing testing and receiving results.[22] However, this understanding may not apply to family members being tested in cascade testing. A study of 297 families of Lynch syndrome probands measured genetic testing–related distress, depressive symptoms, and cancer worries in relation to the amount of time passed since the proband was tested and found to carry a mutation. The study found that cascade genetic testing significantly increased test-related stress and cancer worry as time increased between testing of the proband and other family members. This finding was specifically true for individuals in the same generation as the proband.[23]

BRIEF REVIEW OF HEREDITARY CANCER SYNDROMES WITH PROSTATE CANCER RISK WITH GENETIC COUNSELING IMPLICATIONS

There are multiple genes related to hereditary prostate cancer risk. Some risk levels are better understood than others as this area continues to advance. The following information is based on current knowledge and is likely to evolve over time (**Table 1**).

Hereditary breast and ovarian cancer syndrome

Perhaps best recognized for increased risk of female breast cancer and ovarian/fallopian tube cancers, the *BRCA1* and *BRCA2* germline mutations characteristic of hereditary breast and ovarian cancer syndrome (HBOCS) are also associated with an increased risk for prostate cancer, more so with *BRCA2* positivity.[24–26] *BRCA1* and *BRCA2* are tumor suppressor genes associated with overall genomic stability.

Although the *BRCA1*-associated prostate cancer risk is less well quantified, men with *BRCA2* germline positivity have an approximate 20% to 60% lifetime risk for developing prostate cancer.[27,28] These prostate cancers are often associated with more aggressive disease, including a Gleason score of greater than or equal to 7.[29]

Women with a pathogenic *BRCA2* variant have approximately a 40% to 85% lifetime risk of breast cancer. The lifetime risk for ovarian, fallopian tube, or peritoneal cancer is 17% to 27%.[30–32] In addition, individuals affected with HBOCS have increased risks for melanoma, male breast cancer, and pancreatic cancer.[33] Appropriate high-risk referrals should be facilitated. Autosomal recessive biallelic pathogenic variants in the *BRCA* genes are associated with Fanconi anemia.[34–36]

BRCA2 mutations are associated with a particularly severe form of Fanconi anemia type D1 (FA-D1), which is characterized by bone marrow failure, short stature, abnormal skin pigmentation, developmental delay, and malformations of the thumbs and skeletal and central nervous systems. Risks of leukemia and early-onset solid tumors are significantly increased, with up to a 97% risk of malignancy by 5 years of age.[34]

It was previously thought that inherited biallelic germline positivity for *BRCA1* was an embryonic lethal event. However, survival of inherited biallelic *BRCA1* positivity is possible, and those incidents need to be recognized because these individuals may be destined for a different type of Fanconi anemia (Fanconi anemia, complementation group S [FANCS]).[35,36]

HOXB13-related Cancer Risks

The G84E variant in the *HOXB13* gene is associated with increased risk of prostate cancer and also an earlier age of onset of prostate cancer.[37,38] Inheritance is autosomal dominant. Studies have shown the lifetime risk of prostate cancer to be up to 33%.[39]

Lynch syndrome (hereditary nonpolyposis colorectal cancer)

An increased risk for prostate cancer has been documented in multiple studies of men with Lynch syndrome. Estimates range from an approximately 2-fold to 5-fold increase in risk, or up to 30% depending on the affected Lynch syndrome gene.[6,40,41,42,43,44]

Lynch syndrome is a hereditary cancer syndrome that occurs when 1 or more of 5 mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) has a germline mutation. An indication for this may be found when on immunohistochemistry (IHC) a pathologist finds that 1 or more of the mismatch repair genes is not expressed in a person's tumor.

Men and women with Lynch syndrome have a high risk of developing colorectal cancer, often at younger ages than are seen in the general population.[45] Women with Lynch syndrome also have a high risk for developing endometrial cancer and an increased risk for ovarian cancer.[45]

Patients with Lynch syndrome also have an increased risk of developing a wide variety of other Lynch syndrome–associated cancers, including prostate gastric, small bowel, urinary tract, hepatobiliary tract, brain (usually glioblastoma), sebaceous gland, and pancreatic.[45,46]

Table 1
Autosomal dominant and autosomal recessive characteristics of hereditary prostate cancer genes

Hereditary Prostate Cancer Genes	AD (Monoallelic) Mutation	Increased Cancer Risk and AD Inheritance	AR (Biallelic) Mutation	Risks Related to AR Inheritance
ATM	ATM-related disorders	Prostate, male and female breast, pancreatic	AT	• Ataxia, usually before age 5. Balance problems chorea, myoclonus, neuropathy[81] • Slurred speech and oculomotor apraxia • Telangiectasia, in the eyes and on the surface of the skin • Increased risk of cancer, particularly leukemia and lymphoma • Very sensitive to radiation exposure, including medical x-rays • Life expectancy varies greatly, but affected individuals typically live into early adulthood
BRCA1	HBOCS	Prostate, male and female breast, ovarian/fallopian tube, pancreatic, melanoma	Fanconi anemia (FANCS)	• Developmental delay apparent from infancy, short stature, microcephaly, and coarse dysmorphic features[82] • Laboratory studies show defective DNA repair and increased chromosomal breakage during stress • Some patients have radial ray anomalies, anemia, and increased risk of cancer; patients often have a family history of cancer in family members who have heterozygous mutations
BRCA2	HBOCS	Prostate, male and female breast, ovarian/fallopian tube, pancreatic, melanoma	Fanconi anemia (FA-D1)	• Risks of leukemia and early-onset solid tumors are increased with up to a 97% risk of malignancy by 5 y of age[83] • Short stature, abnormal skin pigmentation, skeletal malformations of the upper and lower limbs, microcephaly, and ophthalmic and genitourinary tract anomalies • Progressive bone marrow failure with pancytopenia typically presents in the first decade, often initially with thrombocytopenia or leukopenia

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Table 1 (*continued*)

Hereditary Prostate Cancer Genes	AD (Monoallelic) Mutation	Increased Cancer Risk and AD Inheritance	AR (Biallelic) Mutation	Risks Related to AR Inheritance
CHEK2	CHEK2-related disorders	Prostate, male and female breast, thyroid, CRC	—	—
HOXB13	Hereditary prostate cancer	Prostate	—	—
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch Syndrome	CRC, prostate, endometrial, ovarian, gastric, small bowel, urinary tract, hepatobiliary tract, brain, sebaceous gland, pancreatic	CMMR-D	• CMMR-D is a rare childhood cancer predisposition syndrome with hematologic malignances, brain/central nervous system tumors, colorectal tumors, and multiple intestinal polyps and other malignancies, including embryonic tumors and rhabdomyosarcoma[46,84] • Many patients show signs reminiscent of neurofibromatosis type I, particularly multiple café au lait macules

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; AT, ataxia telangiectasia; CMMR-D, constitutional mismatch repair deficiency; CRC, colorectal cancer; FANCS, Fanconi anemia, complementation group S; HBOCS, Hereditary Breast and Ovarian Cancer Syndrome; LS, Lynch syndrome.

It is recommended that patients with a diagnosis of Lynch syndrome be managed by a multidisciplinary team with expertise in medical genetics and the care of patients with this condition. Appropriate high-risk clinician referrals should be facilitated. In rare instances, an individual may inherit mutations in both copies of a Lynch syndrome gene, leading to the autosomal recessive condition constitutional mismatch repair deficiency syndrome (CMMR-D).[47] Individuals with CMMR-D often have significant complications in childhood, including colorectal polyposis and a high risk for colorectal, small bowel, brain, and hematologic cancers.[47] The children of Lynch syndrome mutation carriers are at risk of inheriting CMMR-D if the other parent is also a carrier of a Lynch syndrome mutation.

ATM-ASSOCIATED CANCER RISKS

Women who are heterozygous ATM mutation carriers have an increased risk of breast cancer. Men have an increased risk of prostate cancer. Men and women have an increased risk of pancreatic cancer. For men with prostate cancer, ATM genetic mutations are associated with more aggressive prostate cancer.[48,49] Individuals who are homozygous for ATM genetic mutations have an autosomal recessive disorder known as ataxia telangiectasia (AT).[50] AT is a neurodegenerative disorder that causes extreme sensitivity to radiation, increased risk of cancer, early-onset ataxia, and immunodeficiency.[50]

GENES WITH EMERGING EVIDENCE FOR PROSTATE CANCER RISK (*CHEK2*, *NBN*, *BRIP1*)

There are genes that have early and emerging evidence for association with hereditary prostate cancer risk. These genes include *CHEK2*, *NBN*, and *BRIP1*.[51–54] *CHEK2* is a tumor suppressor gene that is associated with increased risk of breast and colon cancer. There are inconsistent data regarding heterozygous NBN genetic mutations and female breast cancer risk. People who are carriers for NBN genetic mutations have a risk of having a child with Nijmegen breakage syndrome. Genetic mutations in *BRIP1* are associated

with increased risk of ovarian cancer. *BRIP1* is also associated with Fanconi anemia complementation group J (FANCJ).

REPRODUCTIVE DECISION MAKING AND GENETIC TESTING FOR INHERITED PROSTATE CANCER

An important part of the genetic counseling process for patients and their families is to understand reproductive implications for themselves and/or their families. As discussed earlier, some of the genes associated with inherited prostate cancer can also be inherited autosomal recessively and this has implications for discussion of reproductive risks for the patient and/or the families.[34–36,47,50] Parents concerned about the possibility of passing on a monoallelic or biallelic genetic mutations to a future child should discuss options for preconception genetic testing and assisted reproduction techniques, such as preimplantation genetic testing with a qualified provider. It is important to counsel patients about the possibility of an autosomal recessive condition in their offspring, and the importance of discussing this with their close family members that are of reproductive age. This discussion should be thoroughly documented in notes shared with the patient and in the patient's medical record.

PSYCHOSOCIAL CONCERNS FOR GENETIC COUNSELING IN MEN

Past literature regarding genetic testing communication and psychosocial implications associated with the cancer predispositions discussed earlier focused almost exclusively on women. This focus was likely attributable to more women receiving genetic testing given the higher level of cancer risk and more medical management options available for women.[55] Although women may be more likely to undergo genetic testing for such genes, research has shown that genetic testing uptake between men and women is similar. Distress following positive genetic testing results is also thought to be similar for men and women, indicating that individuals with a positive result generally show more distress than those that are negative, regardless of gender.[56]

However, prostate cancer genetic testing uniquely focuses on testing men, and many other psychosocial and counseling concerns may differ. From past studies that include both men and women disseminating information about BRCA risk, it seemed that women were often the "point person" in the family and men tended to restrict communication of test results to immediate family members such as spouses, children, and siblings. Specifically, it seemed that men were most concerned about their obligation to share information with their children and grandchildren, rather than other family members.[57] More recent studies show that communication of BRCA-related cancer risk in the family is not gendered and men may take a more active role as disseminators of familial genetic information as well as support providers, and even co–decision makers, than was previously thought. However, although men are taking over more communication roles in the family, many men are neglecting focusing on how they were managing their own risks in consideration of helping their children and close female relatives manage their risks. This finding may indicate a need to educate men about their own risk management in the context of a family-centered approach, especially given their interest in obtaining this information for other family members. These studies also highlighted a need for better education for providers regarding identification of at-risk men as well as a strong desire from patients to participate in support groups where they can connect with other men.[57,58]

CLINICAL IMPLICATIONS

Germline genetic testing

Germline genetic testing is important for men that have a personal and/or family history of prostate cancer.[1] There can be therapeutic implications for men with a personal history of prostate cancer that are found to carry mutations in certain genes. Also, information regarding genetic mutations can provide patients with information to share with family members regarding their cancer risks and the patient's future cancer risk. For men without a personal history of prostate cancer but with a family history of cancer, this information can help inform cancer screening and also provide guidance for other family members. Given the potential impact on therapeutic and cancer risk information, it is important that patients and their families receive the proper genetic counseling and the correct genetic test.

Precision medicine

Germline genetic testing is very important for treatment implications for men with prostate cancer, regardless of family history and age of diagnosis. Approximately 15% to 17% of men with prostate cancer have been shown to have germline mutations.[25,59] For men with metastatic prostate cancer, approximately 12% have a germline mutation.[60]

Metastatic prostate cancer

Germline genetic testing is important for treatment implications for men with metastatic prostate cancer. Research has shown benefits for platinum-based chemotherapy in those with metastatic CRPC and BRCA mutations. In addition, poly-(ADP-ribose) polymerase (PARP) inhibitors have shown responses for men with germline or somatic mutations in *BRCA1*, *BRCA2*, and *ATM*. There have been 2 approvals by the US Food and Drug Administration for use of PARP inhibitors rucaparib and olaparib in the treatment of prostate cancer.[61] Men with loss of DNA mismatch repair or who have Lynch syndrome can be candidates for immune checkpoint inhibitor immunotherapy.[62]

Potential role in active surveillance discussions

Active surveillance is the situation when favorable-risk prostate cancer is actively monitored but treatment is delayed with the understanding that if, based on results from active surveillance, the cancer progresses, treatment will be initiated. Advantages are that men will avoid or delay possible unnecessary side effects of therapy. A significant disadvantage in pursuing this would be missing the window of opportunity for potential cure. Genetic testing results have the potential to be helpful in these discussions when men are making decisions on active surveillance, such as men with *BRCA2* mutations, where prostate cancers can be more aggressive.[49,63] There are also early data with *ATM* mutation carriers.[49]

Implications for screening decisions

Men with *BRCA2* mutations tend to have earlier onset of prostate cancer and it tends to be more aggressive.[49,63] Men with *BRCA2* genetic mutations should consider starting prostate-specific antigen screening at age 40 years, or 10 years younger than the youngest prostate cancer diagnosis in the family.[6] This plan can also be considered with other gene mutations associated with inherited prostate cancer risk.[6]

Somatic testing

Somatic genetic testing is an important piece of care for prostate cancer.[64] Patients and providers need to understand the difference between somatic and germline genetic testing for understanding of meaning for current treatments, future cancer risk for the patient, and implications for family members. Germline genetic testing evaluates genetic mutations in DNA that a patient was born with, whereas tumor testing evaluates acquired mutations in the tumor. Most mutations detected in tumor testing are of somatic origin (the mutation occurred within the formation of the tumor and was not inherited). However, germline mutations can also be uncovered in tumor testing; various studies have reported rates of 3% to 17.5% of patients with tumor testing having germline mutations depending on patient population and specific genes studied.[64–67] It is important during the counseling process that patients understand that tumor testing may uncover germline mutations and thus have hereditary cancer implications.[68,69] Genetic variants that are suspected to be of germline origin from tumor testing need to have confirmatory germline testing. Tumor genetic testing results can help with discussion of platinum chemotherapy and PARP inhibitor therapy.[64] Genetic mutations in tumor tissue may change over time; therefore, this testing might need to be repeated at different stages of the cancer.[64] However, germline mutations do not change over time.

NEW TECHNOLOGIES

As need for genetic counseling for men with prostate cancer increases, it is important to consider alternative delivery models and the use of technologies such as videos and chatbots. These options have the potential to improve access to genetic counselors, facilitate timely genetic testing, and also allow more effective use of genetic counselor time, leading to more tailored counseling sessions.[6,25,70] It has been recommended that additional strategies, such as the incorporation of videos, be used to provide pretest informed consent for men undergoing genetic testing for inherited prostate cancer.[6]

Chatbots are an artificial-intelligence tool that simulate conversation and can be used to gather information before a genetic counseling session, provide pretest genetic education, and assist providers with posttest care coordination.[70] In addition, chatbots can be used to inform relatives of patients with positive genetic testing results to aid in cascade testing.[70]

Studies have shown that patients are willing to incorporate these technologies into their care.[68] However, additional research is needed in order to ensure that these tools provide patients with an adequate understanding and that individual needs are met.[25] In addition, it will be important that these are thoughtfully integrated into cancer genetic counseling models to allow optimal use.[1,25] With increased clinical utility of genetic testing in the setting of prostate cancer, the demand for genetic counseling is increasing.[1] For this reason, more non–genetics providers are ordering their own genetic testing. It is important

for providers who order their own genetic testing to either collaborate with their local genetics teams or use some of these new technologies to aid in providing informed consent to their patients before genetic testing is done and to ensure appropriate genetic testing is ordered.

ETHICAL/LEGAL CONCERNS WITH GENETIC COUNSELING AND PROSTATE CANCER

Nondirectiveness and genetic counseling

Nondirectiveness has historically been considered an essential element of the genetic counseling session.[3,71] Nondirectiveness is when information is presented without leaning toward a particular choice.[3] This approach aims to provide patients with balanced information in order to promote patient autonomy and informed decision making.[3,71,72] Over time, however, the field has moved away from nondirectiveness while still prioritizing patient autonomy.[72] In the emerging area of precision medicine, in which genetic variations are used to direct a more personalized treatment plan, there is a move away from the nondirectiveness approach to genetic counseling.[71–74] It is therefore vital for genetic counselors to balance bioethical principles and, in appropriate situations, provide active guidance to patients.[72]

Autonomy and informed consent

With increasing use and utility of germline genetic testing in the treatment of prostate cancer, it is important for health care providers involved in the care of patients to consider ethical implications for patients and their families. An important component of genetic counseling is informed consent, which allows the patients to have autonomy over choosing whether genetic testing is right for them.

If patients get true informed consent, then they can make an autonomous decision with regard to genetic testing. In order to get consent, the

Table 2
Topics to be covered in genetic counseling for prostate cancer germline testing

Elements of Informed Consent	Description
Purpose of germline testing	Precision therapy, early detection strategies, and/or to identify hereditary cancer syndrome/risk
Possibility of uncovering hereditary cancer syndromes	Depending on the test, it might uncover a hereditary cancer syndrome such as HBOCS and LS (see Table 1)
Panel options	Various multigene panels can be considered for genetic testing. Benefits and risks of each option should be discussed
Potential types of test results	Mutation (pathogenic/likely pathogenic variant). Variant of uncertain (unknown) significance and negative
Potential to uncover additional cancer risks	Multiple gene-specific cancer risks may be identified beyond prostate cancer risk that affects men and their families (see Table 1)
Potential out-of-pocket cost	Not all insurance plans cover genetic testing; some mandate referral to genetic counselor
GINA and other laws that address genetic discrimination	See Box 1, Table 3 on GINA and genetic protections
Cascade testing/additional familial testing	Testing blood relatives for pathogenic variants or additional genetic testing by family history; worry and anxiety that may result from hereditary cancer testing; effect on family relationships
Data-sharing/data-selling policies of genetic laboratories	Each genetic testing laboratory may have unique data-sharing and data-selling policies that patients must be aware of
Privacy of genetic tests	Protection of genetic data from data breach or access by third parties

Abbreviation: GINA, Genetic Information Nondiscrimination Act.

Data From Giri VN, Knudsen KE, Kelly WK, et al. Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol*. 2020;38(24):2798-2811. https://doi.org/10.1200/JCO.20.00046

patients must be competent and understand what they are being told, be able to exercise judgment, be provided relevant information in a clear and understandable way, and be free to make decisions without coercion and outside influence.[75]

Autonomy is the principle that refers to the right of individuals to make health care decisions without interference from others and to make choices that best fit their beliefs and personal values.[76] For this to occur, individuals must understand the consequences of their choices without any interference or influence from others. Autonomy is both a negative (others should not influence choice) and positive obligation (need the proper information to make the choice).[76]

An important way to promote autonomous decision making is with genetic counseling. With help from a genetic counselor or health care provider with expertise in genetics, patients receive the appropriate pretest and posttest counseling and therefore are properly supported in making the right decisions for them.[3] To respect the autonomy of a patient, professionals in health care have an ethical obligation to disclose the right information to ensure that the patient understands, which helps promote adequate decision making.[3,75,76] This process is done successfully by the provider or genetic counselor knowing the social, emotional, and cultural experiences of the patient.[3]

Specifically for getting informed consent with genetic testing for prostate cancer, there are areas of importance that are important to cover before providing genetic testing (see **Table 2**). These areas include the purpose of the germline genetic testing, the chance of finding a hereditary cancer syndrome, the types of genetic testing results, the chance to discover other cancer risks, possibility of out-of-pocket costs for genetic testing, the Genetic Information Nondiscrimination Act (GINA) and other laws that address genetic discrimination (**Box 1** and discussed later), cascade testing, and additional familial testing.[6] Also to be considered are discussion of multigene panel genetic testing options, data-sharing and data-selling policies of genetic testing laboratories, and privacy with genetic testing.[6]

Concerns with Genetic Discrimination The Genetic Information Nondiscrimination Act

Patients and their families often have concerns about genetic discrimination, which is the misuse of genetic information.[3] For providers ordering genetic testing, it is important to be aware of where patients are protected legally and where protection is incomplete.

In 2008, GINA was enacted, which provided some protections for patients regarding their genetic information, which is their genetic testing results or family health history (see **Box 1**).[77] GINA states that it is illegal for health insurance companies to use genetic information to make decisions for a person's eligibility for health insurance or to determine how much the person will pay for health insurance. Also, GINA makes it illegal for employers to demand a genetic test be done and to use genetic information for any pay, firing, or hiring decisions.[77]

GINA has some large gaps, because it does not currently extend these nondiscrimination protections to life insurance, disability insurance, and long-term care insurance.[77] It also does not prevent health insurers from using this information to establish eligibility or premium rates once an individual afflicted with an inheritable disorder has started to show symptoms. GINA also does not

Box 1
Summary of Genetic Information Nondiscrimination Act of 2008 protections

What is covered:

- Health insurance
  - Illegal to use genetic information to make decisions on eligibility or determine cost for health insurance
- Employment
  - Cannot use genetic information for hiring, firing, or pay decisions
  - Cannot demand a genetic test be done

What is not covered:

- Does not apply to:
  - Individuals in the United States military who get their care through the Veterans' Administration[a]
  - Individuals with Indian Health Services[a]
  - Individuals with federal employee health benefits plans[a]
  - Does not prevent discrimination for eligibility or rates once symptoms show
- Does not include protections for life insurance, disability insurance, or long-term care insurance[b]

[a]These plans have protections in place similar to GINA.

[b]Some state laws have protections for genetic discrimination for life insurance, disability insurance, and long-term care insurance.

apply to individuals who have Indian Health Service, federal employees who have federal employee health benefits plans, and members of the United States military who get their care through the Veterans' Administration. There are protections in place with these groups that are like GINA. However, individuals with these types of health care insurance should speak with a case manager or supervisor at their insurance company to obtain a written iteration of that insurers genetic antidiscrimination policy to factor into decision making and avoid potential vulnerability in this area. With regard to employment, GINA also does not extend protection to employees of businesses with fewer than 15 employees. There are some state laws that have additional protections, and this can include protections with life insurance, disability insurance, and long-term care insurance.

Other protections for patients

The Americans with Disabilities Act (ADA) makes it illegal to discriminate in employment, public services, accommodations, and communications based on a disability (**Table 3**).[78,79] Discrimination based on genetic information is also protected by the ADA.[80] There are protections in place for individuals who have a preexisting condition or genetic disease from discrimination with the Health Insurance Portability and Accountability Act and the Affordable Care Act of 2010.

Table 3
Protections with regard to genetic discrimination

Law	What is Protected
GINA of 2008	Provides protections for misuse of genetic information with regard to health insurance and employment
ACA of 2010	Prevents health insurers from discriminating against patients because of preexisting conditions, including genetic conditions
ADA	Illegal for discrimination in employment, public services, accommodation, and communications based on disability
HIPAA	Protects individuals who have a genetic disease or a preexisting condition from discrimination

Abbreviations: ACA, Affordable Care Act; HIPAA, Health Insurance Portability and Accountability Act.

Genetic privacy

Privacy and confidentiality are important in any area of health care; however, there are unique considerations with regard to genetics and genetic testing.[3] Germline genetic testing provides information regarding the patient's risk and also the risk of family members. This information may be stigmatizing, which could put the patient and the family members at risk for discrimination in the workplace or procuring certain types of insurance.[75]

SUMMARY

Somatic and germline genetic testing has become relevant for the treatment of prostate cancer and for identifying hereditary cancer syndromes in affected men and their family members. Genetic counseling is an important component of genetic testing. It is important for treating clinicians to ensure that the patients receive the proper genetic counseling to allow informed decision making. Because of limited access to genetic counselors, alternative models have emerged to aid and even substitute components of the traditional model. However, it is important to ensure all aspects and implications of genetic testing are discussed with patients in both a pretest and posttest setting to facilitate and maintain positive regard and confidence between patient and clinician by avoiding discordant expectations and information when genetic testing is being considered.

CLINICS CARE POINTS

Genetic counseling for prostate cancer

- An important step for germline genetic testing for men with a personal and/or family history of prostate cancer and women with a family history of prostate cancer is genetic counseling.
- Genetic counseling helps maintain positive regard and confidence between patient and clinician by avoiding discordant expectations and information when genetic testing is being considered.
- It is essential to provide informed consent for the patient before undergoing germline genetic testing.
- Posttest genetic counseling includes discussing the implications of germline genetic testing results for the patient and family members and facilitating appropriate high-risk referrals.

- An important part of cascade testing of family members, if a germline genetic mutation is detected, is genetic counseling.
- Genetic counselors provide psychosocial support to patients throughout the genetic testing process.

DISCLOSURE

C. Hyatt was previously a consultant and held stock in GenomeSmart. The other authors have nothing to disclose.

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