Management of Cancer Genetic Testing: A Brief Overview

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GENETIC TESTING

Genetic testing has taken a prominent role in the workup of new cancer diagnoses as well as the management of individuals unaffected by cancer with and without cancer family history. Hereditary genetic testing in oncology is equally applicable to both males and females and is a catalyst for the development of many cancer types including, breast, ovarian, endometrial, colon, pancreatic and prostate cancers. As female breast cancer represents the most common cancer subtype in the US, representing 15% of all new cancer diagnoses, and has one of the largest bodies of genetic research to date, beginning with the discovery of BRCA1 and BRCA2 in 1994, this cancer will be the primary focus of this review.[1,2] Studies have estimated that as many as 1 in 4 women with breast cancer undergo genetic testing.[3] Additionally, genetic testing panels have expanded dramatically in recent years to include as many as 100 genes that predispose patients to breast, ovarian, colon, gastric, pancreatic, skin, and other cancers. Patients can now undergo genetic testing simply by mailing salivary samples from the comfort of their home and be provided with a wide array of information about their genomic risk profile. With the increased utilization of genetic testing as well as the increased knowledge our patients have about the role of genetic testing, providers must familiarize themselves with genetic testing as well as the potential results to determine the best methods of monitoring and screening patients in the future. Genetic counselors play a vital role defining the appropriateness as well as the potential risks and benefits of genetic testing.

Several guidelines have been constructed by various nationally accredited organizations to assist providers in identifying patients for whom genetic testing is appropriate based on identified patient-specific breast cancer risk factors (i.e., the National Comprehensive Cancer Network (NCCN), the American College of Medical Genetics and Genomics, the National Society of Genetic Counselors, the American Society of Clinical Oncology, the American Society of Breast Surgeons). Broadly speaking, the goal of genetic testing is to determine whether an individual harbors a pathogenic variant (mutation) that might predispose him/her/them to an increased risk of a future malignancy. For example, in patients with breast cancer undergoing genetic testing, a pathogenic variant ("positive" result) is identified in approximately 3–10% of patients.[3-5] If a pathogenic variant is not present and the results indicate only benign findings this is defined as a negative result. While the rate of overall pathogenic variants does not differ between individuals of different races, racial/ethnic differences do exist between specific pathogenic variants.[6,7] There also exists a third category of genetic testing results called a variant of unknown significance (VUS). These represent variations in genetic sequencing for which the association with disease risk is not yet well characterized, and, at this time, the vast majority of VUS do not change management for a patient with respect to high-risk screening or preventative surgeries.[8]

GENETIC TESTING IN HIGH-RISK INDIVIDUALS

In accordance with national guidelines, many individuals without a breast cancer diagnosis also meet the criteria for genetic testing which is based on family history and/or other patient risk factors. For example, in patients with a significant family history of breast, ovarian, pancreatic, or colon cancer, it may not always be possible to test affected relatives. For these individuals, genetic testing may still be warranted, and a referral to a genetic professional can be helpful in achieving informed consent. Importantly, a patient may still be deemed at increased breast cancer risk, even in the setting of negative cancer genetic testing. As guided by national recommendation, this lifetime risk can be calculated by incorporating cancer family history, negative genetic test results and other personal risk factors using risk assessment tools such as the Tyrer-Cuzick Risk Calculator and the Gail Model.[9-12] These lifetime breast cancer risk estimates are then used to guide increased surveillance and risk-reducing strategies for breast cancer risk reduction and prevention.[1] The Tyrer-Cuzick risk calculator utilizes various personal, reproductive, and family history characteristics, as well as the patient's probability to harbor a genetic predisposition (if not yet tested) to calculate lifetime breast cancer risk.[9,10] Patients with a lifetime risk >20% qualify for high-risk breast imaging consisting of 6-month staggered mammograms with MRI of the breast.[13] The Gail Model

utilizes similar patient characteristics to calculate both an overall relative risk and a 5-year risk of developing breast cancer to determine the possible use of medication for breast cancer risk reduction.[12] Per NCCN guidelines, patients with a 5-year Gail Model risk >1.7% qualify for consideration of chemoprevention (such as Tamoxifen or Raloxifene), while the American Society of Clinical Oncology (ASCO) recommends consideration of chemoprevention for patients having a 5-year risk of >3%.[14,15] Both models calculate a patient's risk and compares this to the risk of a patient of similar age within the general population. Based on these results patients can be further stratified for increased screening, additional testing, and/or other prophylactic interventions. Additionally, these risk models are often used by insurance companies to determine coverage for these screenings and additional interventions.

NEGATIVE GENETIC TESTING RESULTS

Patients with prior negative genetic testing results may still require further evaluation as ongoing genetic research has identified several novel malignancy-associated genes. It is recommended that all providers consider the role of genetic testing in patients with any newly diagnosed malignancy. For example, patients and families with individuals who were diagnosed with breast cancer prior to 2014 and previously underwent genetic testing with no pathogenic variant identified should consider further evaluation since prior to 2014, high risk genes such as PALB2 and other high and moderate cancer genes were not yet discovered. Additionally, testing also applies to patients with prior negative BRCA1/2 only germline testing, or gene-limited testing. Today there are approximately 23 genes that are associated with an increased breast and ovary risk that are routinely tested and may help to explain a patient's personal or family history that were not available to test in the past.[16,17] Additionally, newer gene-testing techniques such as BRCAnalysis Rearrangement Testing (BART) and RNA analysis also may not have been available at the time a patient previously completed testing, and these advances in technology have been demonstrated to identify other clinically relevant genomic variants that previously could not have been identified.

Additionally, in individuals with current or previous negative genetic testing, it may still be beneficial to test other family members in addition to the patient as negative genetic testing in one individual does not preclude other family members from having genetic mutations as some mutations are *de novo* or may run in the family without having been passed to the patient undergoing testing. It is important that both providers and patients recognize that negative genetic testing results do not mean that an individual will never develop cancer; they simply mean that the patient does not carry the genetic variants tested and, to the best of our knowledge, they are not predisposing them to an increased risk of cancer. However, patients may still have an elevated cancer risk based on personal and/or family history which can be further elucidated through discussions with genetics professionals as well as through risk models.

VARIANTS OF UNKNOWN SIGNIFICANCE

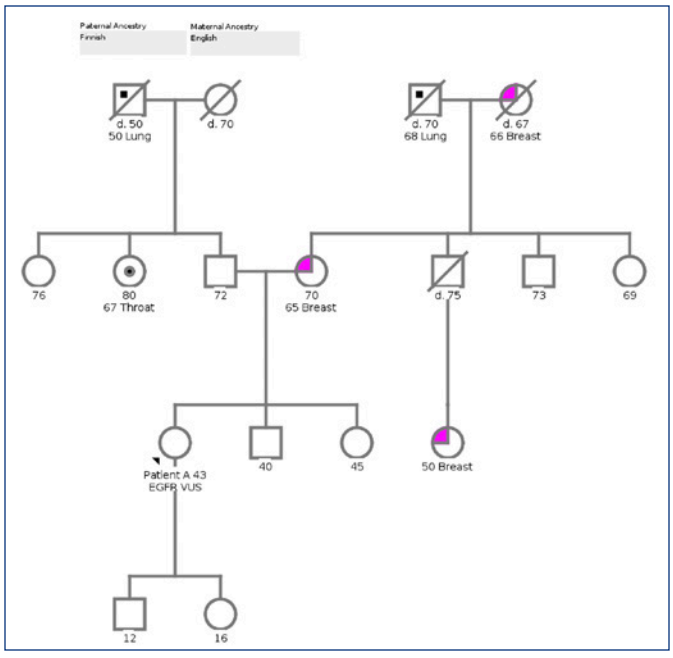
VUS results can be a source of anxiety for patients and present clinical challenges for treating providers. For patients, the knowledge that they harbor a genetic variant, for which the risk of associated malignancy has not yet been defined, can make it difficult to provide reassurance or provide confidence that the patient will not need cancer screenings beyond that of the general population. However, even in the presence of a VUS, it remains important to consider a patient's personal risk factors as well as his/her/their family history when estimating lifetime breast cancer risk. For example, individuals found to carry a VUS having an elevated lifetime or 5-year breast cancer risk as calculated by a recommended risk assessment model (i.e., Tyrer-Cuzick or the Gail Model), management should be based only on this familial risk without influence from their VUS result.[17]

CASE EXAMPLES

Case 1

A 43-year-old patient (Patient A) presents to a genetic counselor referred by her OB/GYN because of a family history of breast cancer and dense breast tissue. She is of Northern European descent. Her family history is collected and presented in **Figure 1.**

Figure 1. Patient A's cancer family history and multi-gene panel genetic testing results.



She undergoes a large panel test and is found to be negative for pathogenic mutations but has a variant of unknown significance in the gene EGFR known as c.797C>A. EGFR is a preliminary evidence cancer gene, meaning there is limited or conflicting evidence about the risks associated with the gene at this point. Preliminary evidence genes do not yet have standardized guidelines and may not be included in all panel tests. The genetic counselor reviews that this VUS has not been well characterized; however, it is reported in the publicly available National Center for Biotechnology Information (NCBI) database by other laboratories, which also classify the finding as uncertain. They review that over 90% of variants are reclassified as benign and, as a result, national guidelines instruct that uncertain variants should not be considered clinically actionable.[24] However, as EGFR is preliminary evidence gene for non-small cell lung cancer, the counselor and patient reviewed the family history of lung cancer, which the patient clarified was related to smoking exposure.[25]

The patient and counselor review the family and medical history to assess if a familial risk score needs to be calculated for appropriate follow-up screening recommendations. Based on the patient's breast cancer history, her medical history is collected for the purposes of accurately estimating her familial risk of breast cancer. Information such as age at cancer diagnoses, her negative BRCA carrier status, age of menarche and menopause, breast density, and parity are collected to calculate breast risk using the Tyrer-Cuzick and Gail models.[9-12] Patient A's Tyrer-Cuzick risk was estimated to be 26.37%, which supports increased breast surveillance defined as yearly breast MRI screening in addition to her annual mammogram. The patient's Gail Model risk was estimated to be 1.28% which falls under the recommended threshold for the consideration of chemoprevention medications for breast cancer risk reduction. Further, the genetic counselor discussed the importance of multi-gene cancer panel testing for other maternal family members as well as her siblings because they could harbor a family mutation that she did not inherit, which would impact the cancer risks of these relatives, close family members as well as her own.

Studies have demonstrated that the rate of variants of unknown significance appears to be higher in Non-White individuals, and the probability of finding a variant of unknown significance increases with the number of genes tested in a multi-gene sequencing panel.[7] Within the state of Rhode Island, the 2020 Census estimates 61.6% of the population to be of Caucasian descent, 18.7% of Hispanic descent, and 12.4% of Black ancestry.[18] Historical records also indicate Rhode Island contains a unique admixture of individuals with unique heritages such as Cape Verde and the Azores.[19,20]

With continued genomic sequencing research, genomic VUS are routinely reclassified. A study conducted between 2006–2018 demonstrated that approximately 6.4% of variants holding various classifications including pathogenic, unknown significance, or benign, were reclassified. In this same study, of those variants that were reclassified, only 0.7% were variants initially classified as pathogenic or likely-pathogenic, and only 0.2% were variants initially classified as benign or likely-benign. However, as many as 7.7% of VUS were reclassified, with 80–90% being downgraded to benign or likely-benign and 10–20% being upgraded to pathogenic or likely-pathogenic which seriously impacted patient medical management.[21,22] This further emphasizes the importance of involving genetic professionals in the management of both established and novel genes identified through multi-gene cancer testing. Genetic testing laboratories will typically contact the ordering physician with details of reclassification leaving the burden to patient contact and updated discussion on the provider who originally ordered testing. It is important for practices to have a plan in place for how to go about recontacting patients to discuss reclassifications as they become available before ordering genetic testing. Legally laboratories do not have an obligation to recontact patients with genetic reclassifications, though some may argue ethically they should; however, ethical and legal perspectives agree ordering physicians must play a role in the notification of their patients in this regard.[23]

POSITIVE GENETIC TESTING RESULTS

When a pathogenic genetic variant has been identified demonstrating increased risks of cancer, patients should be managed appropriately, whether this involves prophylactic intervention, medication for risk reduction, or increased screening. It is important that providers familiarize themselves with hereditary cancer genes that are routinely identified on panel analysis as well as the related recommended medical interventions prescribed when a pathogenic or likely- pathogenic (LP) variant is discovered. Likely-pathogenic variants should be treated as pathogenic; they are defined as being variants that the laboratory has over 90% certainty of being pathogenic.[26] According to the 2023 NCCN guideline, **Table 1** provides a broad description of increased screening and surgical options as related to specific cancer genes. These are the most commonly referenced management guidelines for patients carrying a pathogenic or LP variant and, although these guidelines are elaborate, there are areas that require interpretation from a genetic professional for accurate clinical implementation.[27,28] The NCCN's detection, prevention, and risk-reduction guidelines provide comprehensive medical recommendations that are updated yearly based on currently published literature as well as expert opinion and are accessible online without cost (https://www.nccn.org/guidelines/category).

NCCN guidelines are regularly updated with recommendations for specific genes and should be referenced for up

Table 1. Medical Management for Commonly Inherited Cancer Genes

	Mammogram <40	Breast MRI	BSO***	Increased Frequency of Colonoscopy	Pancreatic Screening
ATM			Consider*		Consider*
BARD1					
BRCA1					Consider*
BRCA2					Consider*
BRIP1	Consider*	Consider*			
CDH1					
CDKN2A					
CHEK2					
Lynch Syndrome**			Consider*		Consider*
NF1					
PALB2			Consider*		Consider*
PTEN			Consider*		
RAD51C					
RAD51D					
STK11					
TP53					

Based on the NCCN Version 1.2023: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (https://www.nccn.org/guidelines/category_2), this is an abbreviated summary of management recommendations for the most common genes associated with inherited cancer risk.

*Recommendations requiring cancer family history review and genetic professional interpretation

** MSH2, MLH1, MSH6, PMS2, and EPCAM mismatch repair genes

*** Bilateral salpingo-oophorectomy

to date recommendations and risks.[28,29] These guidelines recommend ages at which to begin screening and surgical interventions; however, the starting age is sometimes lowered if younger cancers are present in the family that are thought to be related to the identified family variant.

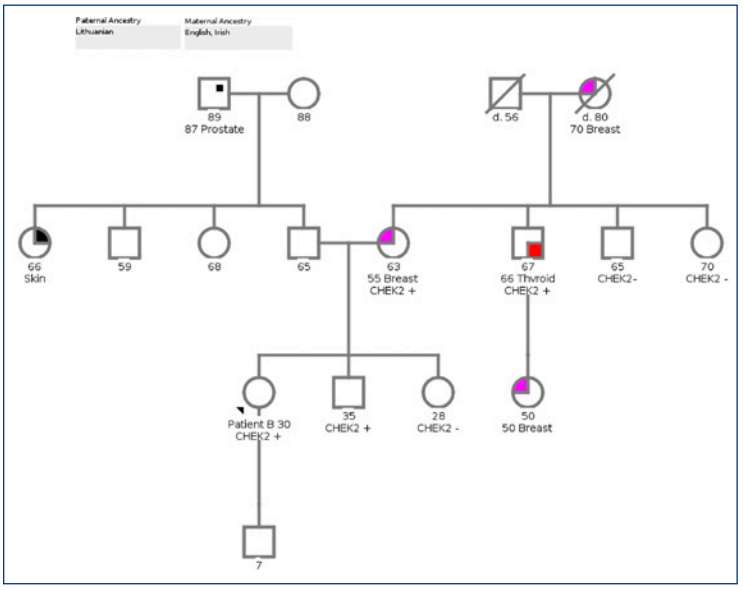
It is important to involve genetics professionals in both the management of established genes and preliminary evidence genes as evidenced by the following case examples.

CASE 2

A 30-year-old patient (Patient B) presents to a genetic counselor referred by her primary care physician because of a family history of breast cancer. She is of Northern and Eastern European descent. Her cancer family history is collected and presented in **Figure 2.**

Patient B underwent cancer genetic counseling and testing and was found to have inherited the pathogenic CHEK2 variant called c.1100delC. This is a well-characterized genetic variant that carries an approximate 40% lifetime risk for the development of female breast and a risk for colon cancer up to 10%.[30-34] As a result, the NCCN Guidelines recommends

Figure 2. Patient B carries a pathogenic CHEK2 variant. The patient's unaffected brother has also inherited the CHEK2 variant however her sister is negative. The patient's mother, diagnosed with breast cancer at age 55, and maternal uncle who was diagnosed with thyroid cancer at age 66, also carry the same CHEK2 variant. This family variant was not passed to the patient's unaffected maternal uncle and aunt.



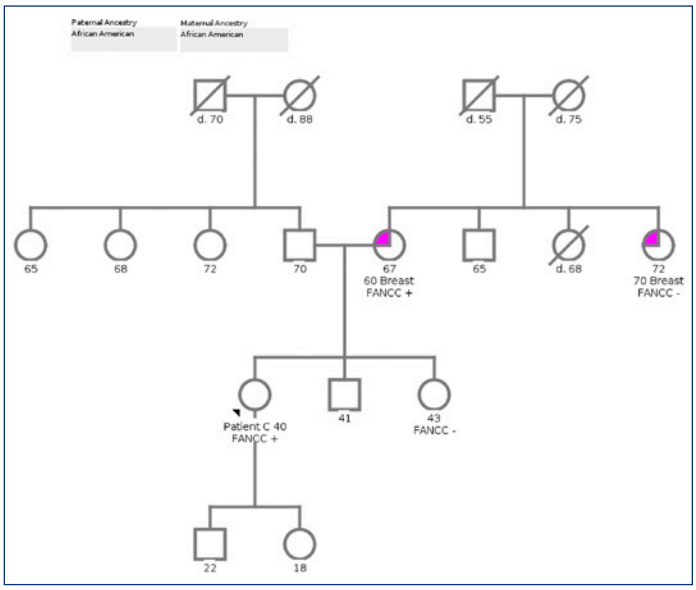
that Patient B consider beginning breast MRI screening, at the age of 30, integrating yearly mammogram at age 40. Additionally, the patient should begin colonoscopy at 40 repeating every 5 years.

The genetic counselor emphasized the importance of family testing due to the autosomal dominant nature of this condition. Therefore, testing a parent was recommended to define from which lineage this variant is traveling. Following her mother's genetic counseling and large panel testing it was discovered that her mother also harbors the family CHEK2 1100delC variant. The patient's uncle who was diagnosed with thyroid cancer was also found CHEK2 positive, and as a result, the counselor discussed with the patient that there is evidence suggesting a change in medical management due to a possible increased risk of papillary thyroid cancer associated with CHEK2 pathogenic variants.[35,36] Therefore, the counselor counseled the patient that evidence and field experts deem it reasonable to her to consider enhanced thyroid screening even in the absence of established guidelines.

CASE 3

A 40-year-old patient (Patient C) presents to a genetic counselor referred by her OB/GYN because of a family history of breast cancer and dense breast tissue discovered on mammography screening. She is of African American descent. Her family history is collected and presented in **Figure 3.**

Figure 3. Patient C's cancer family history and multi-gene cancer test results.



Following cancer genetic counseling and large panel testing, Patient C was found to be positive for the pathogenic variant in the FANCC gene known as c.355_360delTCTCATinsA. This is a protein-truncating variant in a preliminary gene having only early evidence for an increased risk of breast cancer.[37] Although, this variant has been linked to a possible increase in female breast cancer risk,[38] this has not been well documented, and therefore guidelines for increased breast cancer screening have not been established based on a FANCC pathogenic variant alone. The genetic counselor explains the current research and emphasizes the limited evidence. However, as instructed by national guidelines, the genetic counselor proceeds to estimate the patient's lifetime breast cancer risk using the Tyrer-Cuzick model which is high enough to support the addition of yearly breast MRI screening. The implementation of this enhanced breast imaging could potentially diagnose an earlier stage breast cancer ultimately impacting the patient's future health and possibly mortality. The patient was compliant with breast screening recommendations and established a one-year visit in the genetics clinic to discuss updates related to FANCC gene cancer risks and possible medical management changes based on newly acquired evidence.

Take-Away Points
National consensus guidelines (NCCN, ACMGG, NSGC, ASCO, ASBrS) should be utilized by healthcare providers to identify patients qualifying for genetic testing.
Genetic testing results can be positive for a pathogenic variant, negative, or identify a variant of unknown significance.
Patients with prior or current negative genetic test results may benefit from a consultation with a genetic professional to discuss expanded multi-gene panel testing.
Family members may benefit from genetic testing regardless of a relative's negative result since genetic variants are NOT inherited by every family member.
Variants of unknown significance (VUS) are common, (generally) not associated with increased cancer risk and should not change medical management.
Establish a process to recontact patients carrying VUS because important medical management changes may need to be recommended when reclassifications are received by ordering practitioners, at times, years later.
The Tyrer-Cuzick and Gail Models are recommended breast cancer risk assessment tools utilized to determine screenings and/or risk reducing strategies for cancer early detection and prevention.
Genetics professionals play an important role interpreting positive, negative, and uncertain results and patients can be referred at any point during the testing process.

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Conflicts of Interest

The authors report no conflicts of interest.

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