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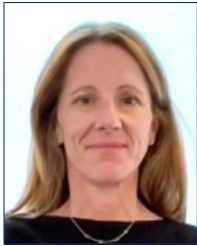
UPDATES *in* CANCER GENETIC TESTING, MANAGING, *and* COUNSELING

GUEST EDITORS: JENNIFER SCALIA, MS; ASHLEY STUCKEY, MD

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SPECIAL SECTION

**Updates in Cancer Genetic Testing,
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On the cover

Scientist holding futuristic smart tablet analysis of DNA structure molecule chain in laboratory of biochemistry.

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Cancer Genetics: From Then to Now

JENNIFER SCALIA, MS
ASHLEY STUCKEY, MD
GUEST EDITORS

The impact of cancer genetics on the field of oncology has dramatically altered the care we provide our patients. In the early 1990s the discovery of BRCA1 and BRCA2 variants laid the framework for cancer genetic counseling and testing as we know it today. Over the last 25 years, the cancer genetics field has grown exponentially from single syndrome testing to the standard of care demanding the simultaneous analysis of over 50 cancer susceptibility genes by routine next-generation sequencing.

The field of cancer genetics has also expanded its purpose, from the simple process of determining individual cancer risks, to assisting patients and their healthcare providers with critical decisions related to surgical choice and treatment. Excitingly, this has led to advances in clinical care, evident through the earlier detection of cancer, decreased mortality due to personalized treatment, and the prevention of cancers that otherwise would have developed. However, due to the high number of individuals now eligible for genetic testing, greater demands are placed on exploring novel methods for the delivery of cancer genetic counseling, especially considering the limited number of trained professionals available. These new applications of genetic testing and the exploration of novel strategies related to cancer counseling are focal points in this everchanging era in oncology genomics. As a result, there are dedicated research efforts examining this constant fluctuation in cancer care, resulting in guidelines to assist practitioners in the translation and application of these complex genetic outcomes.

This issue of the *Rhode Island Medical Journal* (RIMJ) presents a variety of articles devoted to the past, present, and future of cancer genetics, advances in the field, and a glimpse of what to expect next. The manuscript by **JASMINE EBOTT** et al provides a historical background of cancer genetic testing, discusses the criteria necessary for testing referral, describes service delivery models, and provides insight regarding the challenges of insurance coverage.

SANDRA TOMLINSON-HANSEN et al begin with a review of well-established genetic cancer syndromes, including Lynch and Hereditary Breast and Ovarian Cancer Syndrome. This manuscript also describes novel hereditary oncology genes such as PALB2, BRIP1, RAD51C/D, and BARD1, as well as their everchanging, and often uncertain, associated cancer risks.

KATHERINE CRAWFORD et al begin with the intricacies of genetic counseling and testing interpretation and review national guidelines for identifying and screening patients who are at increased risk to develop breast cancer. Finally, they provide informative case studies to illustrate the genetic testing and counseling processes.

The current landscape of gynecologic cancer care is dependent on both somatic and germline genetic testing. **JESSICA DISILVESTRO** et al explain the difference between somatic and germline testing and the implications on current treatment algorithms with respect to FDA-approved or experimental targeted treatments and immunotherapies.

We hope readers enjoy this issue of RIMJ and that it provides cancer genetic updates that will be relevant for clinicians practicing in a wide variety of fields.

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A Genetic Revolution: Cancer Genetic Testing and Counseling

JASMINE A. EBOTT, MD; JENNIFER SCALIA, MS

ABSTRACT

Genetic counseling is a relatively young profession that has advanced rapidly over the last 50 years. The term “genetic counseling” was first coined by Sheldon Reed in 1947 to describe the advice he would give to physicians regarding their patient’s genetic conditions. Today, more than 5,000 genetic counselors are licensed through the American Board of Genetic Counselors. Clinically, genetic counselors practice in a variety of specialties, including pediatrics, prenatal, neurology and psychiatry; however, oncology remains the most common.¹ This article is centered on the most common areas of genetic counseling and addresses the topics of cancer genetic testing, genetic counseling, and explores past and current practices.

KEYWORDS: genetic counseling, genetic testing, service delivery

BRIEF HISTORICAL REVIEW

In the 1970s genetic counseling consisted mostly of reviewing family history and the patient’s personal medical history. From this discussion, patients were given the option of karyotyping and/or cytogenetics pending an institution’s testing capability. In the 1980s fluorescence in situ hybridization (FISH) was developed, allowing for chromosome rearrangements to be detected more easily. These techniques identified large genomic changes such as deletions, duplications, and translocations; however, smaller genetic variants were being missed. It was not until the 1990s when Mullis and Smith won the Nobel Prize in Chemistry for their discovery of PCR technique that launched genetics into a new higher level of clinical diagnostics.²

Directly following the implementation of PCR, Mary-Claire King discovered the Breast Cancer Susceptibility Gene1 (BRCA1) located on chromosome 17q21, which in its altered form, is primarily responsible for 57–66% of early-onset breast cancers and 39–59% of ovarian cancers.³⁻⁵ In 1994, Michael Stratton and Richard Wooster mapped the BRCA2 gene by linkage analysis on chromosome 13.⁶ The BRCA2 gene, like BRCA1, in its altered form, is responsible for 45–61% of breast and 11–20% of ovarian cancers; however, typically with onset at later ages.

The discovery of the BRCA1 and BRCA2 genes launched the field to start routine genetic testing for cancer susceptibility and gave way to current-day, multi-gene cancer panel testing over the last 26 years.⁷ Multi-gene panel testing allows a patient to have multiple genes analyzed from one blood or saliva sample. This type of panel testing is the direct result of the major advancements in genetic testing technology, primarily next-generation sequencing (NGS). NGS is high throughput technology that reads massive parallel sequencing and can generate whole exome or genome results at a much lower cost than prior testing. Most recently, in the early 2000s, RNA analysis was added to multi-gene panel analysis proving an increase in the detection of pathogenic variants in a variety of genes that were not previously detectable with DNA testing alone.^{8,9} In some cases, RNA analysis has been helpful to reclassify variants of uncertain significance (VUS), which are genetic variants undetermined to be benign or pathogenic. Although the addition of RNA testing is thought to detect only a small percentage of missed variants, these novel findings have had a significant impact on patient care.¹⁰

TESTING CRITERIA

The National Comprehensive Cancer Network (NCCN) guidelines are a comprehensive set of guidelines and management strategies created from an alliance of 32 cancer centers in the United States. These guidelines are updated yearly according to the current literature and are most referenced to assist with cancer genetic testing and management for hereditary breast, ovarian, colon, pancreatic, prostate, and kidney cancers. Individuals can meet the outlined criteria for cancer genetic testing in several ways, including: enough of the same or related cancers in the family, rare cancers related to genetic causes, cancers diagnosed at a young age, or a known pathogenic or likely pathogenic variant in the family. As the field of cancer genetics expands due to scientific advancement and better testing technology so does the criteria for being considered for cancer genetic testing.

These NCCN testing guidelines continue to routinely lengthen and have resulted in an elaborate list for healthcare practitioners to reference to understand if their patients may benefit from cancer genetic testing. Although most insurance companies use these guidelines to determine genetic

testing coverage, this is not the case for all policies.¹¹ Some companies have their own guidelines while others place a testing limit on the number of hereditary cancer genes they will cover.¹² On the laboratory side, the restrictions are currently far fewer, with many allowing the inclusion of additional genes without an increase in cost. Because testing and insurance requirements are transient, patients should be counseled to update their practitioner as to any changes to their personal and/or cancer family history since they may qualify for testing or have access to test coverage that they may not have had previously. Additionally, aside from genetic testing, for the unaffected patient national guidelines also recommend risk calculations to determine breast and other cancer susceptibility percentages, which is often based on cancer family history. These cancer-risk estimates help guide providers in counseling their patients regarding appropriate screenings (i.e., younger and/or more frequent colonoscopy) and risk-reducing measures such as the use of aromatase inhibitors for breast-cancer risk reduction.

It is important to note that for patients who meet NCCN's hereditary breast and ovarian cancer testing guidelines, it is no longer standard of care to only analyze the BRCA1 and BRCA2 genes alone. National guidelines now recommend routine clinical testing that includes the analysis of multiple high penetrant genes such as, BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53, as well as moderate-risk genes related to an increased risk of breast and other cancers. At this time, due to the rapid growth of this field with the desire for testing laboratories to gain knowledge, the number of genes analyzed on panel testing typically does not impact the test cost. However, it remains unclear if or how this may change in the future.

GENETIC CONSULTATION-SERVICE DELIVERY MODELS

The typical cancer genetic counseling model involves pre-test counseling, results disclosure, and post-test counseling. Pre-test counseling occurs before a test is ordered. During this meeting, genetic counselors develop rapport and trust with patients. They may discuss many topics, including but not limited to, how the patient does or does not meet testing criteria, the possible cost of appropriate testing, the benefits and limitations of testing, how the test results could impact the patient as well as their family members, and the applicable testing options. Cancer genetic specialists will answer patient questions and review how test results may affect their current medical management regimen as related to cancer risk. A detailed personal and family history will occur, which is critical to ensure that the most appropriate testing is ordered.¹² Discussion about the different types of test result outcomes and, if applicable, the possibility of genetic discrimination will also take place during the pre-test counseling session. Testing options are finalized and

through shared decision-making the best testing modality is facilitated.

Results and post-test counseling vary significantly depending on the outcome of the test. A positive result will lead to a discussion regarding cancer risks, screening implications, inheritance patterns, testing recommendations for family members, and referrals to subspecialists if applicable. Positive results often breed empowerment; however, at times can have psychosocial effects that warrant management through appropriate supportive care resources.¹² Genetic counselors often provide patients with a family letter detailing the results as well as addressing testing and clinical implications for family members. Coordinating cascade testing for at-risk relatives is an additional and important role that genetic counselors take on for their patients.¹² Understanding if relatives carry the family mutation can aid in early cancer detection and prevention, as well as provide relief for those identified not to have inherited the family pathogenetic variant. In the event of a negative result, the patient and genetic counselor review the limitations of the test, the clinical and testing implications for the patient and their family members, as well as the patient's feelings about the outcome. Instructed by medical guidelines, genetic counselors also may provide cancer-risk assessments, even in the setting of a negative genetic test, that can result in additional cancer screenings (i.e., breast MRI, colonoscopy) that may detect cancers earlier or prevent them altogether. The last possible result type is a variant of uncertain significance (VUS), which triggers a discussion between the patient and their practitioners about the uncertainty as it relates to a possible increased risk of cancer and the possibility of reclassification. Fortunately, because these uncertain results are commonly reclassified as harmless, changes to medical management are generally not recommended.

The time necessary for traditional face-to-face genetic counseling in oncology has been challenged by the persistent rise in the demand for these services while having a limited number of trained genetic professionals.¹³ These challenges preceded major genetic advancement in diagnostic testing and treatment, further broadening the need for counseling and increasing the difficulty of accommodating all of those who now qualify for testing. As a result, different methods of service delivery have been adopted in efforts to expand genetic counseling services in oncology which include telehealth, educational videos, counseling using artificial intelligence (AI) technology, as well as the expansion of genetic provider type.¹⁴ One silver lining of the recent COVID-19 pandemic is that it has accelerated the application of telemedicine in the field of genetic counseling. This built upon previous limited examinations of cancer genetic telemedicine services which had already proven to be a viable and non-inferior strategy as compared to traditional counseling methods.¹⁵ AI genetic counseling and the training of non-genetic professionals (i.e., navigators, nurse practitioners)

have also generated positive responses regarding their integration into the education of high-risk cancer patients; however, this continues to be closely studied.¹⁶ With the implementation of novel genetic counseling service delivery methods obstacles also naturally developed that include changes in clinical workflow, insurance reimbursement, and language translation, which are calling for attention.¹⁴ These barriers are being examined in efforts to increase the effectiveness of these new patient education strategies and have exposed the growing need for a transdisciplinary approach to cancer counseling during this era of precision oncology.

Finally, we would be remiss not to mention the direct-to-consumer (DTC) marketing of DNA sequence-based cancer testing, given its popularity in the mainstream population. Importantly, DTC testing is not a replacement for comprehensive, clinically approved, germline genetic testing. These tests do not fully sequence the genes being tested, have a false positive rate of approximately 40%, and vary widely in the information provided and in the accuracy of their interpretations.¹⁷

INSURANCE

The genetic testing cost for individuals meeting the established national testing criteria is commonly fully covered by commercial insurance carriers if the required procedures are followed. Even without insurance coverage, testing companies have made great strides in making testing more affordable with most laboratories offering an out-of-pocket cost of approximately \$250 for large, multi-gene cancer panel testing that includes both DNA and RNA analysis.

During pre-test counseling, before the patient's test is ordered, there is often a discussion about the Genetic Information Non-discrimination Act (GINA). This is a federal law that became active in 2008 and protects individuals from being discriminated against based on their genetic test results by their health insurance carrier and employer. However, this law does not address protection as it relates to other forms of insurance, such as life, long-term care, and disability, as well as for those who are in the military. It is possible that for individuals who receive a positive genetic test result, adjusting or adding one of these policies could be more expensive or they may be denied coverage. For this reason, it is discussed during the pre-test genetic counseling process when patients can choose to delay testing until they are able to update or obtain the desired life or long-term care policy. This is especially relevant for young patients who have never had a cancer diagnosis since they often have not yet considered life insurance enrollment and are commonly without a serious existing or preexisting medical condition.

Lastly, the military are not protected under GINA. The intent was to prevent susceptible individuals from injury or disease exacerbation in the line of duty. Patients' sensitive genetic information can also be accessed when determining

military promotion. Although these practices were put in place to develop a strong military force, the downstream consequences can be psychologically and emotionally catastrophic.

DIVERSITY/EQUITY/INCLUSION

The NSGC Professional status survey (PSS) has sought to understand the demographic composition of the field of genetic counseling throughout the years. Their survey over the last 40 years demonstrated the static landscape of the profession, which mainly consists of Caucasian women under the age of 40.¹⁸ Recognizing this lack of diversity in race, gender, and age is the first step toward changing the discourse and understanding the biases within the field of genetic counseling. There is a substantial amount of scientific evidence that supports diversifying the healthcare field, including the field of genetic counseling, as this will lead to increased access to care, improved patient-provider relationships, greater patient choice, and satisfaction, and ultimately improve the educational experience of the healthcare workforce.

Genetic counseling and the services provided are significantly intertwined with extremely sensitive issues surrounding social and ethical implications as they relate to advances in these fields. Many population groups are skeptical of genetic services due to past harm from the medical community. The community of genetic counselors recognizes the importance of diversity, equity, and inclusion and has taken an active role in confronting the lack of diversity. Specifically, many institutions have sought out community organizers and experts to help provide education and guidance to understand the cultures of the communities they serve.¹⁸

LOOKING TO THE FUTURE

Genetic testing today is commonly performed using germline DNA testing and, due to the rapid expansion of novel genes included in routine testing, the identification of VUS is high (2–44%).¹⁹ Although not routinely performed by all cancer genetic testing laboratories, the addition of RNA analysis is providing the ability to identify intronic variants and classify putative splicing variants not possible with DNA testing alone.

Karam et al demonstrated that RNA genetic testing has great promise in decreasing the number of VUS classifications. Their study showed that RNA testing as an adjunct to DNA analysis clarified 88% of inconclusive results. Although there is promise that RNA testing may be added to routine cancer panel testing in the future, this is currently not the case due to technical limitations within testing laboratories as well as other logistical challenges such as sample collection.¹⁹

CONCLUSION

Genetic counseling is a relatively young field that has had significant implications on understanding cancer genomics, screening, and familial inheritance patterns. The technological advances have allowed us to identify more high and moderately penetrant cancer susceptibility genes, which have translated to the earlier detection and prevention of cancer, testing strategies, guidelines, and recommendations are changing rapidly to align with this quickly advancing field and present new challenges for the healthcare community. The next 40–50 years will likely prove to have many more advances and developments that will allow us to better care for individuals despite their race, ethnicity, age, gender, or creed.²⁰

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Conflicts of Interest

The authors report no conflicts of interest.

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Hereditary Cancer Genes and Related Risks

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KEYWORDS: hereditary cancer, cancer syndromes, Lynch syndrome, clinical features

INTRODUCTION

The recent explosion of knowledge in the field of cancer genetics dates to 1961 when Henry Lynch described an autosomal dominant pattern of gastrointestinal and gynecological cancers in two large families, coining the condition as “Lynch syndrome” as we know it today. Lynch syndrome affects 1 in 279 individuals, representing the most common cause of hereditary colorectal cancer.¹ It then took another 30 years for the discovery of the two, now well-known genes responsible for the majority of inherited breast and ovarian cancers named BRCA1 and BRCA2. Hundreds of ancient pathogenic variants have been discovered to alter BRCA1/2, which have been established to grossly increase cancer risks and cause the familiar condition known as Hereditary Breast and Ovarian Cancer Syndrome (HBOC). Over the last three decades, there has been an exponential growth of knowledge in how genetics can lead to cancer development, and more recently how genetics can help inform specific treatment for a cancer patient. It began with common cancers striking younger patients with strong cancer family histories, which allowed genetic mapping to identify candidate genes and the establishment of what are now well-known cancer syndromes (i.e., Lynch syndrome, HBOC, Li-Fraumeni). Early genetics work led to the identification of genes associated with hereditary cancer conditions such as Cowden Syndrome, Peutz-Jeghers syndrome, and Hereditary Diffuse Gastric Cancer, among others. Over the past 15 years, we have continued to discover more about cancer genetics and have identified other high and moderate risk genes, such as PALB2, ATM, CHEK2, BRIP1, RAD51C, RAD51D, and BARD1. Our understanding of the early discovered tumor suppressor genes such as BRCA1 and BRCA2 has evolved over time, with risk predictions and disease management being constantly refined as our understanding deepens. The National Comprehensive Cancer Network (NCCN) guidelines have come to reflect this changing landscape of cancer care with recent editions more closely tailoring management based on genetic profile.²

The rapidly evolving nature of cancer genetics makes writing a comprehensive review elusive because as data is reported, new research is constantly refining what is known. Therefore, the purpose of this article is to highlight well-established genetic cancer syndromes as well as novel hereditary oncology genes, to review the associated cancer risks, and to emphasize the field’s rapid evolution. It should be noted that because the terms “pathogenic” and “likely pathogenic” are clinically interchangeable, for brevity, only the term pathogenic is used throughout this overview.

LYNCH SYNDROME

Some of the most well-established tumor suppressor genes result in a condition called Lynch syndrome when pathogenic variants are present. Also known as hereditary non-polyposis colorectal cancer (HNPCC), Lynch syndrome is inherited in an autosomal dominant fashion, and therefore commonly evident in each family generation. This hereditary condition is caused by the inheritance of a germline pathogenic variant in one of five mismatch repair genes, MLH1, MSH2, MSH6, PMS2, or less commonly an EPCAM variant which silences MSH2.¹ These pathogenic variants result in increased cancer risks of various types.^{3,4} Initially, our understanding of this condition was limited such that medical management recommendations were identical regardless of the altered mismatch repair gene. Continual research over the past decades, with an even greater focus over the past 10 years, helped clarify the unique cancer risks associated with each Lynch syndrome gene. Depending on the gene, the cancer risks can include colorectal (10% to 61%), endometrial (13% to 57%), ovarian (general population to 38%), gastric (general population to 9%), small bowel (general population to 11%), hepatobiliary (general population to 4%), renal pelvis and/or ureter (general population to 28%), pancreatic (general population to 6%), and central nervous system (general population to possibly as high as 7.7%).⁵⁻⁹ These wide risk ranges are reflective of the varying levels of cancer risk among the five mismatch repair genes. Following the discovery of MSH2 in 1993, cancer risks were initially reported to be the same among Lynch syndrome genes. However, over time it was discovered that each mismatch repair gene results in unique cancer risks or degree of risk. For example, MLH1 carries a colon cancer risk that is

three times that of PMS2^{10,11} and as a result of the increased risk of ovarian cancer in MLH1 carriers there are clinical recommendations for prophylactic ovary removal while the evidence remains insufficient in those who carry variants within MSH6 and PMS2.^{2,5-9} Fortunately, due to the specific genotype-phenotype relationship among Lynch syndrome genes, medical management recommendations are tailored to each Lynch gene, preventing unnecessary medications, screenings, and surgeries.²

Although rare, these genes are also associated with an autosomal recessive condition known as constitutional mismatch repair deficiency (CMMRD). Biallelic pathogenic variants in MLH1, MSH2, MSH6, or PMS2 cause this childhood cancer predisposition syndrome. Colorectal cancer and cancer of the small intestine have been seen in individuals with this condition prior to age 20 and cutaneous findings are like that seen in individuals with neurofibromatosis type I (café au lait macules). Counseling regarding CMMRD is part of the informed consent process, especially for those who are of reproductive age having a partner with a cancer history suspicious for HNPCC.

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME (HBOCS)

HBOCS is also relatively common and caused by well-established tumor suppressor genes, BRCA1 and BRCA2, which were discovered in 1994 and 1995, respectively. Although reported rates vary, breast cancer risk by age 80 for BRCA1 carriers is estimated to be 72% and 69% for BRCA2 carriers in a 2017 cohort study.¹² Additionally, the same study found the risk of contralateral breast cancer to be approximately 40% for BRCA1 carriers and 26% for BRCA2 carriers.¹² Interestingly, the probability of developing cancer varies within each individual BRCA1/BRCA2 carrier (even within the same family) which is likely attributable to other yet to be identified factors including epigenetic modification or environmental factors that are influencing cancer penetrance. Breast cancer risk has also been discovered to be influenced by polygenic risk scores (PRS), which are a collection of single nucleotide polymorphisms (relatively common genetic variants) that together serve to either increase or decrease risk. Individually, these genetic variants have little impact. However, collectively, the impact may someday be determined large enough to alter medical management recommendations. Current research is also investigating how PRS may modify cancer risks, even within those already found to carry an altered cancer predisposition gene such as BRCA1, BRCA2 or CHEK2.¹³ Although identified as the BRCA gene by name, pathogenic BRCA1 and BRCA2 variants are known to increase the risk of additional cancers including ovarian (also fallopian tube and peritoneal cancers) prostate, pancreatic, and cutaneous melanoma. Approximately 48% of BRCA1 and 20% of BRCA2 female carriers

will develop ovarian cancer by age 70.¹⁴ BRCA1 and BRCA2 male carriers have an estimated 29% and 60% lifetime risk of prostate cancer, respectively.¹⁵ Patients diagnosed with pancreatic cancer are more likely than the general population (1.6%) to have a pathogenic variant in BRCA1 (11%) and BRCA2 (17%).^{16,17} BRCA2 may have a link in patients with cutaneous melanoma although studies have produced conflicting results.¹⁸

Pathogenic variants in BRCA2 gene in their recessive form have important reproductive implications as well. In addition to the gene's association with autosomal dominant HBOCS, this gene is also linked to autosomal recessive Fanconi anemia.¹⁹ Far less common, but still reported, Fanconi anemia is also connected to pathogenic variants in the BRCA1 gene.²⁰

Different types of autosomal recessive Fanconi anemia are linked to other hereditary cancer genes; however, the type associated with biallelic pathogenic BRCA2 variants, Fanconi anemia type D (FANCD1), is particularly severe in comparison. Characteristics include bone marrow failure, short stature, abnormal skin pigmentation, developmental abnormalities in multiple organ systems, and early-onset cancers (acute leukemia and solid tumors). The cumulative probability for malignancy is estimated to be up to 97% by age 6.^{19,21-24} Therefore, discussions with a mutation carrier of reproductive age include the option of testing his/her partner to clarify their future children's risk of Fanconi anemia.

COWDEN SYNDROME

This is a rare autosomal dominant disorder with an incidence of approximately 1 in 200,000 resulting from germline variants in the PTEN gene.²⁵ It is notably associated with hamartomas,²⁶ along with a higher incidence of breast cancer (60%),²⁷ thyroid disease (30–68%),^{28,29} thyroid cancer (3–10%),²⁶ and other malignant and nonmalignant features. One study found the cumulative lifetime risk of any type of cancer in patients diagnosed with Cowden syndrome was 85% overall, with females found to have an increased cancer risk compared with males.³⁰

LI-FRAUMENI SYNDROME (LFS)

LFS is another well studied but rare genetic cancer syndrome and is caused with a germline pathogenic variant in the TP53 gene.³¹ This cancer syndrome is generally associated with a devastating lifetime cancer risk of essentially 100% and often strikes at a young age.³² The breadth of associated cancer risk spans from soft tissue sarcomas, breast cancer, colon cancer, adrenocortical carcinoma, brain tumors,³³ gastric cancer,³⁴ acute lymphoblastic leukemia,³⁵ and possibly melanoma.³⁶ Red flags for this condition include breast cancer diagnosed prior to the age of 31, a diagnosis or family history of LF associated tumors before age 45, or pediatric

acute lymphoblastic leukemia.³⁷ Interestingly, large panel testing is uncovering families who do not fit this expected phenotype, highlighting the value in multi-gene panel testing as well as ongoing research of what are thought to be rare cancer syndromes.

PALB2

Similar to BRCA1/2 genes, PALB2 is considered a high-risk gene in its association with hereditary breast cancer. It was originally identified as a BRCA2-interacting protein critical for BRCA2 function and subsequently discovered to encode proteins involved in BRCA1 and RAD51 pathways. It is a partner and localizer of BRCA2, and deleterious PALB2 variants increase similar cancer risks.³⁸ Inherited in an autosomal dominant fashion, loss of function variants are associated with an approximate 35% increased risk of breast cancer by the age of 70 compared to women without a pathogenic variant in this gene.³⁸ There is strong evidence that pathogenic PALB2 variants are also associated with a small increased lifetime risk of ovarian cancer (up to 5%) as well as pancreatic cancer (5–10%).³⁹ There is also emerging evidence for the increased risk of male breast, prostate, and possibly colorectal cancer.⁴⁰ However, more research is needed. Pathogenic variants in the PALB2 gene are also associated with autosomal recessive Fanconi anemia type N (FANCN), giving it the same reproductive considerations as BRCA1 and BRCA2 carriers.³⁸

ATM

Research shows pathogenic ATM variants are associated with moderately increased risk for the development of breast cancer in women. A meta-analysis suggests the lifetime risk for breast cancer by age 80 in those with pathogenic ATM variants is 33%.⁴¹ Pancreatic cancer risk is also increased in ATM carrier to a lifetime risk of approximately 5% to 10% compared to the 1.6% general population risk.⁴² Lastly, studies connect this gene with an elevated risk of ovarian cancer (2–3%); however, in comparison, this is much lower than the 20–48% risk associated with pathogenic variants found in BRCA1 and BRCA2.⁴³

ATM variants can result in the development of autosomal recessive ataxia telangiectasia, which is typically identified in early childhood with the development of progressive cerebellar ataxia. Ataxia telangiectasia is also associated with oculomotor apraxia, telangiectasias of the conjunctiva, and frequent illness due to immunodeficiency. Childhood leukemia and lymphoma are the most common malignancies.⁴⁴

CHEK2

Inherited in an autosomal dominant fashion, pathogenic variants in the cell cycle checkpoint kinase 2 (CHEK2) gene

have a cumulative lifetime risk for breast cancer estimated to range from 28% to 37%, categorizing it as another moderate risk gene.^{43,45} Although the risks remain unclear, studies have shown CHEK2's possible connection with colon, thyroid, and prostate cancers, among others.^{46,47}

BRIP1

Pathogenic variants in this gene have a clear association with autosomal dominant risk for ovarian cancer and type J autosomal recessive Fanconi anemia (FANCI).⁴⁸ Breast cancer risk has been suggested, but not supported by subsequent research. The lifetime risk for developing ovarian cancer by age 80 is estimated to be 5% to 10%.⁴⁹

RAD51C/RAD51D

These genes are involved in homologous recombination and DNA repair. Pathogenic variants in RAD51C and RAD51D were initially identified as causing an increased risk for ovarian cancer, which is estimated to be 10–15% and 10–20% respectively. More recent studies have shown a strong association with an increased lifetime risk of female breast cancer (20–40%) changing breast screening recommendations.⁵⁰ RAD51C also has reproductive implications given its association with type O autosomal recessive Fanconi anemia (FANCO).⁵¹

BARD1

Pathogenic variants in the BRCA1-associated RING domain 1 (BARD1) gene are known to be associated with an increased risk of breast cancer. The risks were recently refined to 20–40%.⁵²

CONCLUSION

We acknowledge this review does not include descriptions of all hereditary cancer syndromes and genes. Therefore, a more exhaustive list is summarized in **Table 1**, which includes inherited cancer genes associated with hereditary colorectal polyposis (APC, MUTYH, and others) as well as genes related to rare inherited cancer syndromes such as Hereditary Diffuse Gastric Cancer Syndrome (CDH1), Birt-Hogg-Dube Syndrome (FLCN), and Von Hippel-Lindau Syndrome (VHL).

The progression of knowledge surrounding hereditary cancer syndromes continues to change our understanding of cancer risk for all those affected. As a result, there are positive influences on clinical management. Through genetic awareness and targeted screening cancers can be diagnosed earlier, intervened on, and even prevented.⁵³ As cancer genetic testing becomes more common due to increased media and medical attention, as well as from the rapid

Table 1. Hereditary Cancer Syndromes

Gene	Disorder	MOI	Associated Cancers/Clinical Features
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch syndrome	AD	Cancers: CRC, endometrial, ovarian, gastric, renal pelvis and/or ureter, bladder, small bowel, pancreas, biliary tract, CNS, skin
APC	Familial adenomatous polyposis (FAP) Attenuated-FAP (AFAP)	AD	Clinical Features: Polyposis Cancers: CRC, small intestine, stomach, hepatoblastoma, pancreatic, thyroid, brain Other manifestations (FAP only): desmoid tumors, osteomas, CHRPE
MUTYH	Polyposis syndrome	AR	Clinical Features: Colorectal and extracolonic polyps Cancers: CRC, duodenal
AXIN2, BMPR1A, GREM1, POLE, POLD1	Polyposis syndromes	AD	Clinical Features: polyposis Cancers: CRC
NTHL1	Polyposis syndrome	AR	Clinical Features: polyposis Cancers: CRC
BRCA1, BRCA2	HBOC	AD	Cancers: Breast, ovarian, pancreatic, prostate, melanoma
TP53	Li Fraumeni syndrome	AD	Cancers: premenopausal breast, soft-tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma
PTEN	Cowden syndrome		Clinical features: macrocephaly, thyroid lesions, hamartomatous polyps, lipomas, cutaneous lesions Cancers: breast, endometrial, thyroid, renal
CDH1	HDGC	AD	Cancers: diffuse gastric, lobular breast
PALB2	HBOC	AD	Cancers: breast, ovarian, pancreatic
ATM	HBOC	AD	Cancers: breast, ovarian, pancreatic
CHEK2	Hereditary breast	AD	Cancers: breast, colon
BRIP1	Hereditary ovarian	AD	Cancers: ovarian
RAD51C	HBOC	AD	Cancers: breast, ovarian
RAD51D	HBOC	AD	Cancers: breast, ovarian
BARD1	Hereditary breast	AD	Cancers: breast
FLCN	Birt-Hogg-Dube	AD	Clinical features: lung cysts, pneumothorax, renal tumors, skin lesions (fibrofolliculomas/trichodiscomas) Cancers: renal
MEN1	MEN1	AD	Clinical features: endocrine tumors
RET	MEN2	AD	Cancers: medullary thyroid
SDHx	PGL/PCC	AD	Clinical features: paraganglioma, pheochromocytoma
VHL	von Hippel-Lindau syndrome		Clinical features: hemangioblastoma, pheochromocytoma, renal cysts, pancreatic cysts, endolymphatic sac tumors. Cancers: renal

MOI: Mode of Inheritance; AD: autosomal dominant; AR: autosomal recessive; CRC: colorectal cancer; CNS: central nervous system; GI: gastrointestinal; HBOC: Hereditary breast and ovarian cancer syndrome; HDGC: Hereditary Diffuse Gastric Cancer; MEN1: Multiple Endocrine Neoplasia type 1; MEN2: Multiple Endocrine Neoplasia type 2; PGL/PCC: Hereditary paraganglioma-pheochromocytoma syndrome

influx of direct-to-consumer genetic testing, the greater the demand on healthcare practitioners to increase their knowledge and resources to access genetic services. Although access to updated national guidelines greatly assist practitioners in understanding who is at risk for an inherited cancer syndrome and how to manage those testing positive, the interpretation and management are nuanced and complex. Therefore, additional methods of service delivery for pre-test education continue to be investigated to accommodate the increasing number of individuals qualifying for genetic testing with the small number of trained professionals available. As this gap widens it becomes more important to stay current in this rapidly advancing field to fulfill the

duty of best clinical care and to address practice limitations with education, available resources, and patient referral if deemed necessary.

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Management of Cancer Genetic Testing: A Brief Overview

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KEYWORDS: cancer genetic testing, variant of uncertain significance, familial risk, preliminary risk gene

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

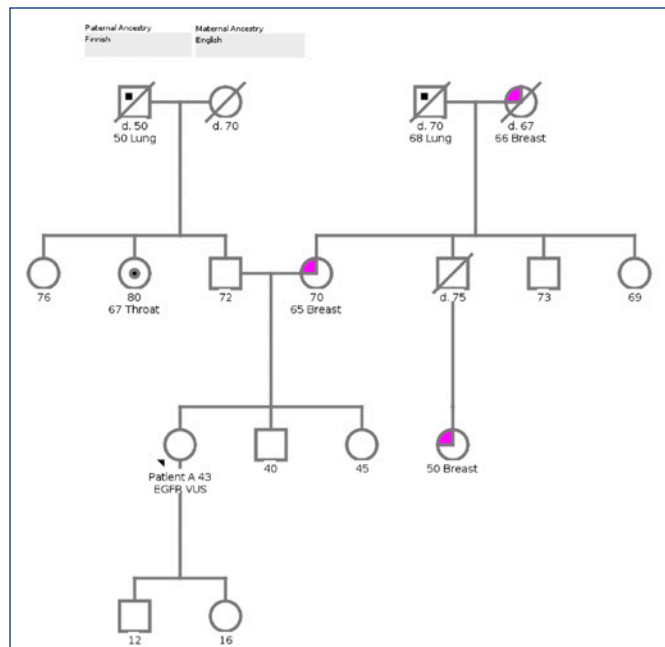
VUS results can be a source of anxiety for patients and present clinical challenges for treating providers. For patients, the knowledge that they harbor a genetic variant, for which the risk of associated malignancy has not yet been defined, can make it difficult to provide reassurance or provide confidence 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

	Mammo-gram <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.

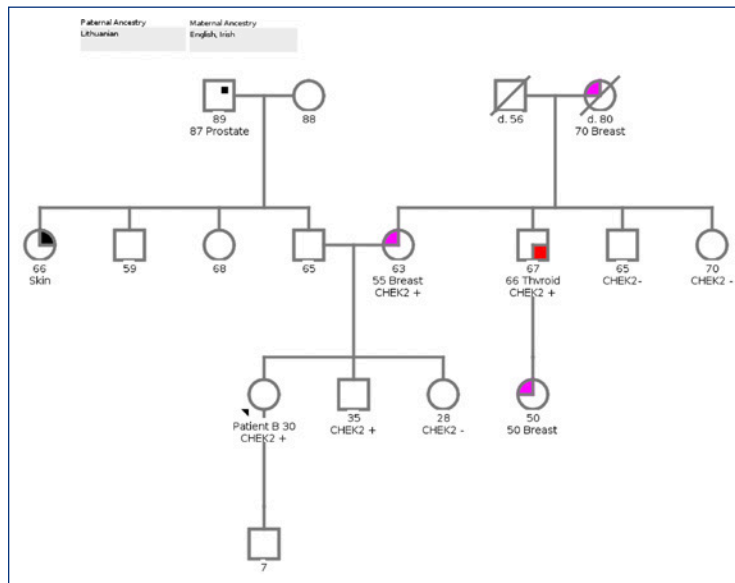
It is important to involve genetics professionals in both the management of established genes and preliminary evidence genes as evidenced by the following case examples.

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.



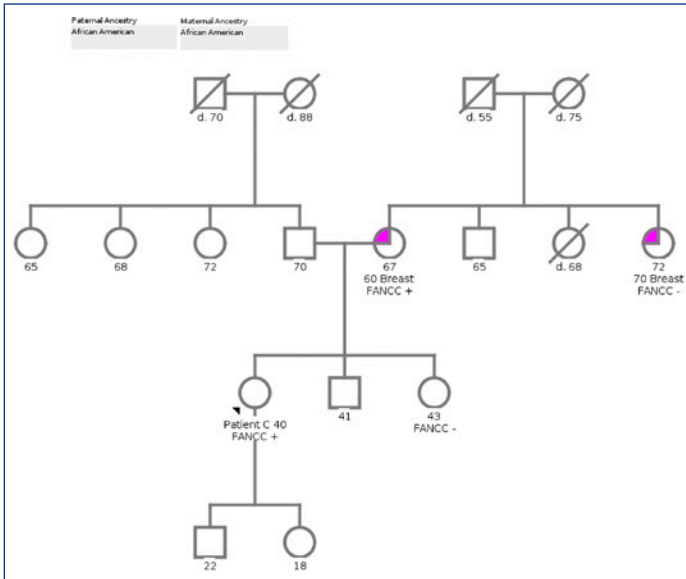
that Patient B consider beginning breast MRI screening, at the age of 30, integrating yearly mammogram at age 40. Additionally, the patient should begin colonoscopy at 40 repeating every 5 years.

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_360delTCT-CATinsA. 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.

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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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Germline vs. Somatic Genetic Testing: Their Increasing Use and Application

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KEYWORDS: genetic testing, germline, somatic, genomic, targeted therapeutics

INTRODUCTION

With the rise of personalized medicine within oncology, genetic testing has become increasingly important. At the time of initial diagnosis, many patients are candidates for upfront evaluation of their germline (inherited) DNA and/or their somatic (tumor) DNA, depending on their cancer type. These results can determine therapy in the adjuvant, maintenance, and recurrent setting. Germline and somatic variants also can have a significant impact on a cancer prognosis, determining additional cancer risks and recommended screening. In addition, this information can help to determine if family members have an elevated risk to develop cancer and if so, management options for early detection or risk reduction.

Prior to the implementation of wide-panel genomic sequencing of tumors, multiple techniques were used to identify oncogenic markers such as immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) which are still commonly used today. In 2013, Foundation Medicine first published validation of their somatic next-generation sequencing assays which demonstrated a high sensitivity of 95-99% as well as a three times higher identification rate of actionable mutations compared to diagnostic tests.¹ The most common tumor specimens analyzed in this study were lung (18%), breast (14%), and cancers of unknown primary (9%). With the introduction of this technology, there has been a rapid increase in the use of somatic genomic sequencing over the past decade.

This article is dedicated to describing the differences between germline and somatic testing and reviewing their applications. Although both testing methods are used within a variety of cancer types, for the purposes of this article, we will focus primarily on their application within gynecologic oncology.

GERMLINE TESTING

An individual's germline DNA is formed by combining half of the mother's DNA from the egg and half of the father's DNA from the sperm. Pathogenic variants (PVs) are passed from parent to offspring and since that variant is present at the time of fertilization, it gets copied into every cell of the body. Many hereditary cancer syndromes follow autosomal dominant inheritance patterns, which translates to a 50% chance for a parent to pass the PV to their offspring.

Germline genetic testing is typically performed on lymphocyte DNA from blood or a combination of lymphocyte and buccal cells from saliva. There are some cases where blood and saliva cannot be used to perform germline testing. For example, DNA extracted from blood or saliva of a patient that has been diagnosed with a hematological cancer may be tumor DNA and therefore not indicative of a germline variant. A blood or saliva sample from patients who have undergone an allogeneic bone marrow transplant would analyze the DNA of the donor rather than the patient. In these cases, a skin punch biopsy with fibroblast culturing is recommended to obtain DNA.²

Germline testing is the standard test offered to patients with a personal and/or family history of cancer suggestive of a hereditary cancer predisposition syndrome. Germline PVs account for approximately 5-10% of all cancers. When an inherited PV is identified, it predicts what types of cancers a patient is at risk to develop. The type of cancer risk changes depending on the affected gene because genes are assigned different functions depending on the body part.

In gynecologic oncology, the National Comprehensive Cancer Network's (NCCN) criteria for germline testing for ovarian cancer are less stringent as compared to endometrial cancer. All patients with epithelial ovarian cancers, regardless of age at diagnosis, are recommended to pursue germline testing, whereas patients with endometrial cancers must be diagnosed under age 50, have a synchronous or metachronous Lynch syndrome-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain, biliary duct, and small intestine) or have a family history of endometrial cancer.^{2,3} Although every year the NCCN's genetic testing criteria broadens to encompass more patients with endometrial cancer, studies such as Levine et al involve an even wider population recommending germline testing for all endometrial cancers regardless of age at diagnosis and family history.⁴

SOMATIC TESTING

Somatic testing is performed on surgical pathology or a cancer tissue biopsy to elucidate the genomic profile of cancer cells (sequencing hundreds of genes) and assess for PVs that can be targeted for treatment. While germline genetic testing identifies PVs that exist within every cell in the body, somatic testing identifies PVs that exist within cancer cells only. The cancer cells may have distinct genetic mutations, new and different from the patient's germline cells, that are responsible for malignant proliferation. The potential for the discovery of additional genetic mutations within the cancer cells beyond which exists in the patient's germline is why this separate testing is recommended. The main questions being asked are: What is the genetic profile of the tumor and how is it different from the genetic profile of the patient's germline or normal tissue? Does one, or both, have a genetic variant that led to the patient's cancer diagnosis and do we have treatments to target it?

The commencement of The Cancer Genome Atlas (TCGA) project in 2006 by the National Cancer Institute and National Human Genome Research Institute deepened our understanding of the molecular characteristics of cancer.^{5,6} They developed a genomic database of over 20,000 primary tumors spanning 33 cancer types. Analysis of this data introduced us to new subclassifications within cancer types, as well as revealed important genomic similarities between cancers of different primary organ types. The TCGA project, in addition to the International Cancer Genome Consortium, laid the foundation for subsequent research on the clinical implications of these genomic alterations and their use as targets for novel therapeutics.⁷ For an assortment of cancer types, there are a wide array of targeted treatments and immunotherapy, in addition to numerous genomic-based clinical trials that are available to patients depending on their individual tumor genomic profile.

GENETIC TESTING AND TREATMENT

Precision medicine is a growing field utilizing genomic sequencing to therapeutically target patient-specific genomic alterations. Within gynecologic oncology, there is a growing need for targeted therapy and immunotherapy for both initial cancer treatment as well as maintenance therapy. Given these impactful clinical applications, healthcare providers should be aware of when germline and somatic genomic testing is appropriate for their patients.

In February 2022, the American Society of Clinical Oncology (ASCO) published a clinical opinion statement on the indications for somatic genomic testing in patients with metastatic or advanced solid tumor cancer types.⁸ This statement supports performing somatic multigene panel genomic sequencing in patients if there is a known biomarker-linked approved therapy for that cancer. For example, the FDA-approved PARP inhibitor, olaparib, is used within germline

or somatic BRCA1/2 mutated patients with ovarian, pancreatic, prostate, or HER2-negative breast cancer. The guidelines also recommend multigene panel genomic sequencing in solid tumors to assess microsatellite instability status and tumor mutational burden for the application of the FDA-approved immunotherapy, pembrolizumab. Somatic genomic sequencing for these purposes should be performed at appropriately certified laboratories.⁸

In the setting of recurrent disease, somatic testing is increasingly important with the expanding targeted therapy and immunotherapy applications. Particularly with the introduction of tissue and tumor site-agnostic treatments, such as pembrolizumab, which was the first FDA-approved tumor-agnostic treatment in 2017, multigene panel genomic sequencing can provide options for alternative therapies, especially in successive lines of treatments.⁸ Evaluation of a multigene panel genomic sequencing not only evaluates the application of treatments already FDA-approved but also allows for assessment of eligibility for biomarker-selective clinical trials. Utilizing the National Institutes of Health's clinical trial database (<http://clinicaltrials.gov>) can potentially offer patients a wider scope of treatment options, if not restricted by location, and should be considered in the clinical decision-making process.

GENETIC TESTING AND HEREDITARY CANCER SURVEILLANCE

Somatic testing alone can reveal genetic variants that are suggestive of a germline PV. This should then prompt the need for subsequent germline testing due to its association with additional cancer risks for the patient and their family members.^{2,3} A 2019 study of 2,308 patients diagnosed with a variety of tumor types found that 5% of patients had PVs on somatic testing that triggered referral for germline testing.⁹ Of the 41% who completed germline testing, 74% had a germline PV identified.⁹ The somatic genes found to harbor a PV prompting follow-up germline testing included, but are not limited to, BRCA1/2, PALB2, BRIP1, MSH2/6, and RAD51C/D. When this occurs, the patient should be referred to a genetic counselor/professional for follow-up counseling and germline testing. For example, a physician may order somatic genomic testing for a patient with recurrent metastatic endometrial cancer (not meeting guidelines for somatic testing in the upfront setting) that identifies a PALB2 pathogenic variant. Assuming she did not previously qualify for germline testing based on age or family history, she is now a candidate for blood or saliva testing to assess for the presence or absence of this somatic PALB2 variant. If the PALB2 variant is also identified within her germline this would increase cancer risks for both the patient and her family members who would benefit from additional medical care that could detect cancers earlier or reduce the risk of developing cancer.

Knowing that a patient has a germline PV provides additional treatment options, but it can also identify when high-risk cancer surveillance is necessary. The NCCN provides recommended medical management guidelines for the majority of established hereditary cancer genes/syndromes.^{2,3} These guidelines allow providers to offer patients more intense screening such as breast imaging every 6 months (BRCA1/2) or colonoscopy screening every 1–3 years (Lynch syndrome).^{2,3} The guidelines also provide the option of risk-reducing surgeries such as removal of the ovaries (i.e. BRCA1/2, BRIP1, RAD51C/D)² which has demonstrated a decrease in morbidity and mortality.¹⁰

Genetic testing not only benefits the patient but also has a meaningful impact on the family. Discovering that a germline PV exists allows for cascade testing to identify relatives who also carry the family PV and, therefore, have an increased risk of cancer. The majority of known hereditary cancer genes travel in an autosomal dominant inheritance pattern. This means that the patient’s first-degree blood relatives have a 50% chance of also inheriting the same PV. Once a relative undergoes counseling and testing and is found to carry the known family PV, the respective recommendations for increased screening, and medical or surgical management can be made. Additionally, in most cases, relatives who test negative for an established family PV (true negatives) do not need risk reducing surgeries or high-risk surveillance which can be a relief to that individual.

Cancers arise when two events cause genetic damage which stops the gene from functioning, known as the Two-Hit hypothesis. The two genetic events could be a combination of two random events (sporadic cancers) or one inherited germline PV and one random event (germline cancers). Paired somatic and germline testing can help to clarify what cancers were caused sporadically. Two PVs identified in tumor tissue (double somatic PVs) with negative germline testing have been shown to cause sporadic cancers.¹¹ Similar to true negative testing, relatives of patients with sporadic cancers would not have to pursue high-risk screening but may tailor screening based on the family history. For example, individuals with no known hereditary cancer syndrome, but whose first-degree relative was diagnosed with colon cancer, should pursue colonoscopies at age 40 (or 10 years prior to the relative’s age of diagnosis) and repeat this exam every 5 years compared to the general population screening recommendation that starts at age 45 and repeats every 10 years.¹²

INFORMED CONSENT

Multiple organizations have written position statements regarding informed consent for genetic testing, which include discussing incidental or secondary findings as well as the accuracy and limitations of genetic testing.¹³⁻¹⁵ With both somatic and germline genetic testing, it is common to identify incidental PVs that have no association with the

primary reason for testing. For example, informed consent should include making patients aware that the identification of a germline PV, and thus germline validation testing, may be recommended based on their therapeutic somatic test result.

Accuracy and testing limitations are important components that need explanation before patients make a decision about genetic testing. Not all labs offering somatic testing have the option of including germline validation testing. Laboratories having only the capability to perform somatic testing can inform the ordering provider that a PV may be germline; however, additional samples will need to be collected and sent to a secondary laboratory for confirmatory germline analysis.

Both germline and somatic testing can miss identifying PVs. In 2022, Terraf et al found that somatic testing alone failed to detect 10.5% of clinically actionable germline PVs.¹⁶ On the other hand, Hampel et al (2021) identified that 3.5% of germline negative endometrial cancers had double somatic PVs in the mismatch repair genes.¹⁷ For this reason, providers should consider the combination of upfront somatic and germline genetic testing in order to provide accurate and effective patient care.

TREATMENT IMPLICATIONS AND GYNECOLOGIC ONCOLOGY

Ovarian cancer is an example within gynecologic oncology in which both germline and somatic testing are recommended at the time of initial diagnosis. Per the NCCN guidelines, all patients with a personal history of epithelial ovarian cancer should undergo germline genetic testing.² Additionally, multigene somatic sequencing is increasingly important for prognosis and treatment of ovarian cancer and should be performed upfront at the time of diagnosis. There is growing evidence of favorable outcomes with targeted therapy in both BRCA1/2 and homologous recombination deficient tumors. For patients diagnosed with ovarian cancer having the inability to repair double-strand DNA breaks, 13–21% harbored a germline BRCA1/2 mutation, and an additional 6–7% had somatic BRCA1/2 variants.^{8,18-21} Furthermore, approximately 50% of high-grade serous ovarian carcinomas are homologous recombination deficient.²²⁻²⁴

Poly-ADP ribose polymerase (PARP) is an important protein involved in DNA repair pathways, particularly in base excision repair of single strand breaks.²⁵ PARP inhibitors block these repair pathways, ultimately leading to double strand breaks and targeted cell death of tumors with homologous recombination repair deficiencies, such as BRCA1/2 mutations.²⁶ This mechanism has been the focus of numerous studies on the various PARP inhibitors within several tumor types.

The PARP inhibitor olaparib is FDA-approved for use as upfront maintenance therapy in patients with advanced

high-grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer and either a germline or somatic BRCA1/2 variant. This approval was based on the 2018 data reporting an incredibly promising progression free survival advantage with a 70% lower risk of disease progression or death.²⁷ The SOLO1 randomized, double-blind, placebo-controlled, international phase III trial recently published powerful overall survival data on olaparib as upfront maintenance therapy.²⁸ Patients were randomly assigned olaparib 300 mg BID or placebo for up to 2 years after demonstrating a complete or partial response after platinum-based chemotherapy. At 7 years, 67% of patients receiving olaparib were alive, compared to 46.5% of patients receiving placebo (HR 0.55, 95% CI, 0.40 to 0.76; P<0.0004). Patients receiving olaparib had a median time to first subsequent treatment of 64 months, compared to only 15 months for patients receiving placebo (HR 0.37, 95% CI, 0.28–0.48).²⁸ The potential to achieve long-term remission is an exciting breakthrough and further highlights the importance of identifying those harboring BRCA1/2 germline and somatic variants early in their treatment course to provide all eligible patients the opportunity towards a cure.

TAKE HOME POINTS

- Germline genetic testing evaluates a patient’s inherited DNA while somatic genetic testing evaluates tumor DNA. A patient may qualify for germline and/or somatic genetic testing based on family history or a specific cancer diagnosis.
- Somatic genomic sequencing has increasing clinical applications for cancer prognosis and treatment. Based on results, patients may be candidates for either FDA-approved or experimental targeted treatments and immunotherapies.
- Somatic test results may prompt germline testing. These incidental findings must be included in the informed consent process.
- Genetic counselors/professionals are valuable resources to help determine and facilitate the necessary genetic testing, interpret test results, and work closely with the patient’s healthcare team to implement the most effective cancer risk-reducing and preventive plan.

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Conflicts of Interest

The authors report no conflicts of interest.

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