A Genetic Revolution: Cancer Genetic Testing and Counseling

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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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