3-11-2019

Hereditary Cancer Genetic Panel Testing: A Review of the Literature

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Recommended Citation

Harris, G. P., & Hutson, S. P. (2019). Hereditary Cancer Genetic Panel Testing: A Review of the Literature. SAGE Open. https://doi.org/10.1177/2158244019835936

Original Research

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SAGE Open
January -March 2019: 1–10
© The Author(s) 2019
DOI: 10.1177/2158244019835936
journals.sagepub.com/home/sgo
SAGE

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Abstract

Cancer genetic testing (CGT) is a powerful diagnostic test that improves cancer prevention and early detection among individuals at high genetic risk of cancer. Since the completion of the mapping of the Human Genome Project, CGT has become increasingly available in the clinical setting. However, as gene discovery and sequencing technology improve, the impact of these advancements on patients is less understood. The use of multigene cancer gene panel tests has become increasingly prevalent; as such, the likelihood of incidental or inconclusive findings has increased. The author conducted a literature review to outline the science on CGT methods, the psychosocial responses to testing among patients, and the unique role of nurses in this process. A significant gap in the literature exists regarding multigene cancer genetic panel tests and the associated experiences and decision-making processes among individuals who have had testing. Future research will specifically explore the experiences of young women with breast cancer who have undergone hereditary cancer risk assessment genetic panel testing that reveals incidental or inconclusive findings.

Keywords

genetic testing, panel testing, genetic counseling, psychosocial oncology, hereditary cancer

Introduction

In 2018, some 1,735,350 people in the United States will be diagnosed with cancer (American Cancer Society, 2018). The emotional stress of receiving a cancer diagnosis is a devastating setback. Physical and psychological impairments associated with the discovery of cancer may lead to an inability to carry out normal, everyday activities for any person. More specifically, female patients under the age of 45 who are diagnosed with cancer may experience increased psychosocial distress attributed to the feeling of having much life left to live and many responsibilities to maintain. Women under 45 are most commonly diagnosed with breast, colorectal, and lung cancers (American Cancer Society, 2018). As many as one in 19 women in the United States will be diagnosed with some form of cancer before the age of 45 (American Cancer Society, 2018).

Fortunately, in the past 20 years, cancer detection and early prevention measures have improved significantly. Providers now employ cancer genetic testing (CGT) for early identification of hereditary cancer syndromes, allowing for earlier identification and prevention of cancer (Baylin & Jones, 2012; Matloff, Bonadies, Moyer, & Brierley, 2014). More than 200 hereditary cancer syndromes have been identified in cancer research. These syndromes account for 5% to 10% of all cancer, with breast, colon, and/or endocrine neoplasia being the most highly penetrant. A susceptibility to inherited cancer is suspected with characteristics such as a diagnosis of the same type of cancer in two or more relatives on the same side of the family, more than one generation affected, and/or early age of diagnosis (Nagy, Sweet, & Eng, 2004).

Still, the presence of a cancer-predisposing mutation in a family does not guarantee cancer development. Other factors such as patterns of inheritance determine cancer development. Autosomal dominant inheritance causes a single altered copy of a gene to increase a person's likelihood of cancer development. In this case, the person's parent may also present effects of the mutation. Autosomal recessive inheritance gives a person an increased risk of cancer only if they inherit a mutated copy of the gene from both parents. Finally, X-linked recessive inheritance occurs when a female with a recessive cancer-predisposing mutation on one of her X chromosomes passes a copy of the gene to her son, who will then only have a copy of the altered chromosome and a resulting increased risk of cancer (National Cancer Institute, 2016). With increases in knowledge of hereditary cancer

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syndromes, CGT has become a standard of care in oncology and, increasingly, primary care settings.

The Role of CGT

CGT is a powerful means to discover deleterious mutations in a patient's genes. In its simplest form, this technology allows for patients to know whether they are at increased risk of cancer beyond general population risk. It also allows individuals to make informed choices about cancer risk reduction, and if cancer is diagnosed, that it is done so at earlier stages (National Cancer Institute, 2016).

The primary reason people choose to undergo CGT is because of personal and/or positive family history of cancer (Burt & Neklason, 2005; Facing Our Risk of Cancer Empowered [FORCE], 2016; Gomy & Estevez Diz, 2013). A family history of a blood relative with a known mutation in a gene that increases cancer risk, a blood relative with two or more primary breast cancers, two or more relatives with breast cancer on the same side of the family with at least one diagnosed before age 50, or a blood relative with ovarian cancer are among various risk factors that increase a person's likelihood of having a mutation themselves (FORCE, 2016). In addition, anyone with a personal or family history of three or more cancers such as pancreatic, prostate, melanoma, sarcoma, adrenal, brain, leukemia, uterine, or other cancers also maintain a higher risk of deleterious mutation themselves (FORCE, 2016; Stoffel & Chittenden, 2010) Other reasons for undergoing CGT include having a family member or members who have had cancer at a younger age than normal (50 years or younger) or a family history of a known genetic mutation (Burt & Neklason, 2005; FORCE, 2016; Stoffel & Chittenden, 2010). Ethnicity is another determining factor in choosing to partake in genetic testing as well as any physical evidence that may be linked to an inherited cancer. For example, individuals who are Eastern European Jewish have a higher risk of carrying specific mutations in *BRCA1* and *BRCA2* genes (American Cancer Society, 2018).

The approach to genetic testing is analogous for all hereditary cancer syndromes (Burt & Neklason, 2005). A detailed review of the patient's family history is first obtained to identify any probable genetic mutations (Burt & Neklason, 2005; National Cancer Institute, 2016).

Patients then attend genetic counseling, where informed consent for testing for a genetic mutation is obtained (American Academy of Pediatrics Committee on Bioethics, 2001; Gomy & Estevez Diz, 2013).

A Brief History of Genetic Testing

The study of genetics began in 1865 when Gregor Mendel introduced the fundamental laws of inheritance (Mendel, 1865). Mendel's contributions along with significant advances in technology in the 20th century led to events such as the proposition of a relationship between chromosomes and cancer by Theodor Boveri, a description of the double helix structure of DNA by James Watson and Francis Crick, and the innovation of the Sanger sequencing method by Frederick Sanger (Boveri, 1929; Sanger, Nicklen, & Coulson, 1977; Watson & Crick, 1953). These discoveries allowed scientists to develop genetic tests for conditions such as Down syndrome, cystic fibrosis, and muscular dystrophy (National Institutes of Health, 2010). By 1990, the Human Genome Project was launched to reveal a complete map of the human genome (Durmaz et al., 2015). The first report of the Human Genome Project claimed that the human body had 30,000 to 50,000 genes (Durmaz et al., 2015). The final report of the Human Genome Project in 2003 revealed 93% of the human genome and declared that the human genome contained 20,000 to 25,000 protein-coding genes (Durmaz et al., 2015). During the late 1990s, the study of genetics focused on the central role of epigenetic processes regarding disease causation (Baylin & Jones, 2012). Before long, genetic testing became a standard procedure for clinical indications such as screening newborns for health conditions (National Institutes of Health, 2010). In 1996, *BRCA1* and *BRCA2* were cloned, shifting the focus of genetic testing to cancer (Matloff et al., 2014).

In the past 10 years, CGT has evolved from a rare, costly subspecialty to a practice that is a standard of care in the cancer management continuum (Baylin & Jones, 2012; Matloff et al., 2014). Recent gene sequencing techniques have revolutionized the ability of scientists to recognize nucleosome positioning and how changes in these contribute to cancer (Kouzarides, 2007; Matloff et al., 2014). CGT is used today to confirm hereditary cancer syndrome diagnoses and serves as a path toward cancer prevention and early treatment (Burt & Neklason, 2005).

Genetic panel testing is a widely used measure of modern CGT. More specifically, genetic cancer panel testing is a process used to examine several different cancers and risk variants simultaneously (Hiraki, Rinella, Schnabel, Oratz, & Ostrer, 2014; Meldrum, Doyle, & Tothill, 2011; Santos et al., 2012). Because of their cost-effectiveness, panel tests permit scientists to sequence multiple targets associated with cancer risk (Hiraki et al., 2014). In addition, panel testing allows for the testing of large amounts of gene targets to clearly understand a patient's risks (Hiraki et al., 2014). Panel testing yields various results that are explained to patients during genetic counseling: positive, negative, true negative, uninformative negative, false negative, variant of unknown significance, and benign polymorphism (National Cancer Institute, 2016).

Gene expression signatures are another up-and-coming tool used to reveal clinically significant characteristics of biological samples. These signatures are used to recognize not only mutations in single genes but also distinct subtypes of tumors. Gene signatures can identify cellular responses to their environment and predict cancer outcomes, aiding in cancer monitoring and treatment (Chang et al., 2011). A

study conducted by the Champalimaud Clinical Center in Lisbon, Portugal, examined MammaPrint, a 70-gene signature test, to determine its ability to predict clinical outcomes for patients with early-stage breast cancer. This study examined 6,693 women with early-stage breast cancer and, using the 70-gene signature test, determined their genomic risk. Clinical risk was also identified using a modified version of Adjuvant! Online. Women with a high clinical risk and low gene signature risk who were not treated with chemotherapy were found to have a 5-year rate of survival without metastasis, only 1.5 percentage points lower than those women who did receive chemotherapy. The study concluded that some 46% of women with breast cancer and a high clinical risk may not require chemotherapy (Cardoso et al., 2016). The use of gene signatures alongside panel testing provides a broadened view of a patient's cancer recurrence risk to best construct their treatment plan.

Despite great advances in CGT, no test has perfect predictability. The quality of cancer genetic tests is described by how well the test determines who truly has the disease (sensitivity) and by how well the test tells who does not have the disease (specificity). A very sensitive test will detect even the slightest abnormal finding. Highly sensitive tests may leave cases of cancer undetected, but may also result in false-positive results. A test with high specificity will have fewer false-positive results, but will have more false negatives (Susan G. Komen Foundation, 2018).

Currently, research is being carried out to identify stronger avenues of detecting and treating cancer among those who are found to carry deleterious genetic mutations. In the future, CGT and panel testing will continue to hold a crucial role in cancer care. It is expected that the cost of genetic testing will continue to decline such that, eventually, a person's entire genome will cost less than US$1,000 to sequence (National Institutes of Health, 2010).

The Nurse's Role in Genetic Testing

At the forefront of holistic patient care, nurses' responsibility in CGT is becoming increasingly important. Nurses play a crucial role in genetic-based practice and take on numerous tasks such as gathering family history, assisting with informed decision making, and providing genetic counseling (Badzek, Calzone, Jenkins, Culp, & Bonham, 2013; Lea, 2008; Pasche & Absher, 2011). While there are specific credentials required to be an advanced practice nurse in genetics, Bachelor of Science in Nursing (BSN) programs across the United States are in the process of revision to incorporate essentials of the study of genetics into the curriculum (Phillips, 2006). Overall, however, genetics is becoming less of a specialty discipline and more of a standard factor in everyday holistic nursing care (Umberger, Holston, Hutson, & Pierce, 2013).

Very early in the CGT process, oncology nurses are responsible for gathering patients' cancer family history. During this time, nurses serve as an educator for patients, teaching them about the importance of reviewing family history information when considering genetic testing (Lea, 2008). Nurses also construct pedigrees from family histories to assess hereditary and nonhereditary disease risk factors (Phillips, 2006). Finally, nurses are responsible for identifying potential genetic conditions or predisposition to disease based on family history (Phillips, 2006).

Another important role of many oncology nurses is assisting with the informed patient decision-making process. After a patient's family history is assessed and discussed, it is crucial that patients be informed of the risks and benefits of CGT, the possible outcomes of testing, and choice about deciding to undergo testing (American Academy of Pediatrics Committee on Bioethics, 2001; Lea, 2008). Nurses are involved in all of these steps (Lea, 2008).

Advanced Practice Nurses in Genetics (APNGs) are specifically trained in the care of patients with genetic illnesses. These advanced practice nurses assist patients and families by assessing hereditary factors related to genetic conditions such as cancer. They also serve as a liaison between patient and physician for patient care management. APNGs acquire their positions by first earning a BSN degree and then attaining a Master of Science in nursing in which they gain specialized clinical training in genetics (American Nurses Credentialing Center [ANCC], 2016).

Genetic counseling is often facilitated by advanced practice nurses before and after CGT to translate genetic information to patients (Lea, 2008). Genetic counselors educate patients on hereditary cancer syndromes as well as the overall CGT process and its outcomes. Patients are informed of cancer prevention and management techniques, and available research on their cancer and are provided with resources to aid them in their journey (National Cancer Institute, 2016). Genetic counselors also educate patients on the physical and psychological risks of learning their genetic test results, along with the possibility of an uninformative result (National Cancer Institute, 2016). Genetic counselors typically first earn a bachelor's degree in biology, social science, or nursing and later go on to participate in a master's program accredited by the American Board of Genetic Counseling (National Society of Genetic Counselors [NSGC], 2016).

Historically, registered nurses have left much of genetic practice to advanced practice nurses. Baccalaureate programs in nursing, however, are constantly undergoing revisions to incorporate further training in genetics into the curriculum. Currently, required genomic-related competencies for registered nurses are separated into four categories: nursing assessment, identification, referral activities, and provision of education, care, and support (Phillips, 2006; Umberger et al., 2013). BSN programs educate students to consider genetic influences when considering appropriate interventions and to evaluate the impact of treatments on patient outcomes (Lea, 2008). Registered nurses are also responsible for the facilitation of referrals for specialized

genetic services for patients as needed. Unfortunately, challenges such as a lack of appreciation for the significance of genetics in nursing practice, faculty unpreparedness, and a lack of emphasis of genetics in RN licensure examinations hinder the progress of genetics in nursing education (Umberger et al., 2013). As CGT becomes more advanced, nurses will be increasingly responsible for communicating genetic information as an everyday part of cancer patient care.

Psychosocial Implications of CGT

With constant improvements in technology and medicine for oncology and genetics, participating in genetic testing will become more and more commonplace for standard cancer prevention and treatment. As the number of patients who undergo CGT increases, so increases the necessity of understanding CGT. Specifically, it is important to further examine the psychosocial impacts the results of genetic testing have on patients (Patenaude & Julian-Reynier, 2008). Numerous studies have been conducted to assess different aspects of these psychosocial implications among different groups of people.

Potential Psychosocial Concerns Associated With CGT

Several authors have found that genetic testing leads to notable psychosocial implications. In fact, it has been suggested that approximately one quarter of those who undergo CGT acquire some level of distress, anxiety, or depression (Pasacreta, 2003). One study conducted by the Swansea University ($n = 194$) found that up to three quarters of those who participated in their study reported concerns related to their experience with testing (Bennett et al., 2012). Of these concerns, over two thirds of participants reported apprehension and concern about how their families would react to their results, implications for family members of an increased risk result, and how participants would personally cope with an increased risk result. Other responses included concerns regarding the decision-making process based on testing results and the overall impact of genetic risk of cancer on lifestyle (Bennett et al., 2012).

Along these lines, another study conducted by the Netherlands Cancer Institute ($n = 127$) sought to identify specific psychosocial concerns related to genetic testing and counseling and to create a questionnaire designed to recognize these problems in individuals undergoing genetic testing in the oncology setting (Eijzenga et al., 2014). The survey developed in the study, the Psychosocial Aspects of Hereditary Cancer (PAHC) questionnaire, contained 26 questions organized into six major categories of identified problems: genetics, practical issues, family, living with cancer, emotions, and children (Eijzenga et al., 2014). The study concluded that when used in conjunction with the Distress Thermometer—a visual analog scale ranging from 0 to 10 to describe one's distress—the PAHC questionnaire was an effective first-line screener for psychosocial problems in candidates for genetic testing. Using these measures, the study found need for increased psychosocial counseling after testing (Eijzenga et al., 2014; Tuinman, Gazendam-Donofrio, & Hoekstra-Weebers, 2008).

While the studies above demonstrate noteworthy results regarding concerns associated with CGT, several of them possess important weaknesses as well. A few studies had small or unrepresentative samples (Pasacreta, 2003). Other studies were not performed in the United States (Bennett et al., 2012; Eijzenga et al., 2014; Tuinman et al., 2008). Furthermore, a few of the studies were carried out qualitatively, which may provide less insight into statistical evidence (Bennett et al., 2012; Eijzenga et al., 2014).

Predictors of Potential Psychosocial Concerns Associated With CGT

Various factors have been attributed to a greater likelihood of acquiring psychosocial problems for patients who participate in CGT. According to one study in the Netherlands ($n = 165$), researchers searched for prognostic factors to predict which counselees were most likely to develop psychological problems after genetic testing (Voorwinden & Jaspers, 2016). Male and female participants above the age of 18 with a 50% or greater risk of *BRCA1/2* or Lynch syndrome were surveyed at three different points to determine factors contributing to their emotional distress after testing (Voorwinden & Jaspers, 2016). Overall, authors concluded that worries regarding cancer after genetic testing were best predicted by preexisting cancer worries, a positive deleterious result, a high-risk perception of getting cancer, and being single (Voorwinden & Jaspers, 2016).

Hirschberg, Chan-Smutko, and Pirl (2015) also cited numerous existential risk factors that contribute to stress and anxiety regarding CGT. For example, a history of depression, use of medication, and high levels of distress at the time of testing resulted in greater levels of distress after genetic testing (Hirschberg et al., 2015). Whether or not a person had lost a family member to a hereditary cancer, especially if an individual lost a parent before the age of 13, was another strong indicator of potential distress. Coping styles and familial relationships also affected how a person handled the stress of results from genetic testing. Those with positive family relationships were more likely to adhere to counseling recommendations and displayed fewer symptoms of distress (Hirschberg et al., 2015). Finally, perceived risk and distress at baseline played a large role in predicting stress, especially in patients who overestimated their level of risk (Hirschberg et al., 2015).

A study conducted in Hong Kong, China (n =76) sought to investigate the factors that predict psychological resilience in adults undergoing genetic testing for hereditary colorectal cancer. Researchers used a longitudinal design to test participants on four different occasions throughout 1 year (Ho, Ho, Bonanno, Chu, & Chan, 2010). This study concluded that baseline hope was a significant predictor of resilience for those participating in genetic testing and suggested further interventions to increase hope levels in patients to ease potential psychosocial harm caused by genetic testing (Ho et al., 2010).

Of the studies mentioned above, the most significant limitation is that much of the literature surrounding risk factors for psychosocial distress associated with CGT is from other countries (Bennett et al., 2012; Ho et al., 2010). Further research in the United States may be necessary to determine the significance of these findings related to the American culture.

Potential Psychosocial Benefits Associated With CGT

Many investigators have found that while psychosocial implications may accompany CGT, symptoms such as depression and anxiety are no higher in patients who undergo testing than those who do not. A study conducted in 2011 was designed to determine impacts of genetic testing on the psychological distress and cancer worry caused by genetic testing, as well as perceived advantages of testing claimed by pancreatic cancer and melanoma patients (n = 60; Aspinwall, Taber, Leaf, Kohlmann, & Leachman, 2013). Results showed that participants who underwent genetic testing demonstrated decreases in anxiety, depression, and cancer worry long term due to the knowledge of their test results (Aspinwall et al., 2011). One participant noted feeling "more at ease for [his or her] children's sake" and that genetic testing granted "choices and options for the better about taking steps to prevent" cancer (Aspinwall et al., 2011, p. 284). Other perceived benefits of genetic testing claimed by participants included the informational benefit of increased knowledge about melanoma risk and its management, as well as the benefit of improved health behaviors and likelihood to increase practice of genetic screening (Aspinwall et al., 2011).

Another study that focused on patients undergoing genetic testing for Lynch syndrome revealed that positive genetic test results often lead to transient psychosocial repercussions. However, patients appeared to have no long-term genetic testing–related depression or anxiety (Galiatsatos, Rothenmund, Aubin, & Foulkes, 2015). In fact, most signs of depression and anxiety related to genetic testing were seemingly normal by 6 to 12 months (Galiatsatos et al., 2015).

According to the previously mentioned study by Ho et al. (2010), hereditary colorectal cancer patients who participated in this study exhibited little to no signs of depression or anxiety the year after disclosure of their genetic test results (Ho et al., 2010). It was concluded that a majority of those tested for hereditary colorectal cancer were psychologically resilient and exhibited little to no signs of depression immediately after genetic testing (Ho et al., 2010). In fact, only 8.7% of participants exhibited elevated symptoms of anxiety and another 7.2% symptoms of depression caused by genetic testing. Furthermore, it was estimated based on the results of the study that the percentage of participants exhibiting test-related anxiety and depression would decrease to 7% to 9% by 12 months (Ho et al., 2010).

Voorwinden and Jaspers (2016) found that immediately after genetic testing, counselees with an unfavorable result demonstrated no more emotional distress than those with a favorable result. It was not until 4 to 6 weeks after testing those counselees with an unfavorable result demonstrated increased levels of stress and concern regarding their genetic testing results (Voorwinden & Jaspers, 2016).

Finally, a study measuring qualitative and quantitative outcomes of females with breast cancer found genetic testing to be psychologically advantageous to patients (Schlich-Bakker, ten Kroode, & Ausems, 2006). The investigators concluded that females who participated in genetic testing and genetic counseling experienced reductions in anxiety, especially when counseling was tailored to their specific needs (Schlich-Bakker et al., 2006).

Limitations surrounding the studies regarding psychosocial benefits associated with CGT include small sample size (Aspinwall et al., 2011) and the lack of exploration regarding various dynamics between nonmutation carriers such as affected family member reactions, coping mechanisms of partners of patients affected by a mutation, the impact of a diagnosis on career, and professional goals. In addition, further research is necessary on the psychosocial aspects of patients who decline CGT (Galiatsatos et al., 2015).

Ethical Implications of CGT

With constant advances in technology, CGT continues to become less expensive and more affordable for many patients at risk of cancer. Panel testing, in particular, is a widely used tool for assessing genetic risk of multiple types of cancer. Panel testing is a popular form of personalized medicine that gives patients an objective response to understand their level of risk for cancer (Hiraki et al., 2014). Despite its benefits, however, panel testing presents various ethical dilemmas that must be taken into consideration (Hanoch, Miron-Shatz, Rolinson, & Ozanne, 2014; Hermel, McKinnon, Wood, & Greenblatt, 2016; Hiraki et al., 2014; Ormond et al., 2010; Surbone, 2001; Tabor et al., 2012; Tavtigian, Greenblatt, Goldgar, & Boffetta, 2008).

Defining the target population for panel testing is one challenge of using this approach. First, few people who wish to undergo genetic testing even meet the criteria to warrant testing of their specific cancer risk (Hiraki et al., 2014). For example, the first step in CGT is assessing the family history

(Gomy & Estevez Diz, 2013). Without a family history of hereditary cancer, many people are ineligible for panel testing altogether, although they may still have concealed risk-increasing mutations that would be uncovered from genetic testing (Hiraki et al., 2014). Furthermore, it is difficult to determine who has the right to the information of an individual's panel testing results. Antonella Surbone of Sloan Kettering Cancer Center in New York (2001) asks, "Does the daughter of a cancer patient have the right to know her mother's BRCA status?" (p. 153). There is great ethical dilemma between the determination of who has the right to know the results of an individual's genetic testing and the importance of maintaining an individual's confidentiality (Surbone, 2001).

Another challenge in panel testing lies within the issue of informed consent. Informed consent requires that a patient be presented with adequate information so that they are fully aware of potential risks and benefits of a treatment before agreeing to proceed (Ormond et al., 2010). Unfortunately, providing a patient with all the details of potential strengths and limitations of panel testing may lead to information overload, inhibiting a patient's proper decision-making ability (Hiraki et al., 2014). One study aimed to qualitatively gain understanding about patient expectations and perceptions regarding the potential risks and benefits of genetic testing (Tabor et al., 2012). This study found that traditional approaches to informed consent were not appropriate for genome sequencing and that these approaches often lead to excessive burden on participants. Increased knowledge of genetic risk can be life-altering, and obtaining ethical informed consent for panel testing is an area of controversy (Ormond et al., 2010).

Along these lines, genetic testing for children and adolescents presents another ethical dilemma. A study by Botkin et al. (2015) reviewed the ethical, legal, and social implications of genetic testing in children. There are various heritable conditions for which genetic testing provides highly predictive information about a patient's future health status. When it comes to children, this information leads to concerns regarding stigma and discrimination against children in some circumstances (Botkin et al., 2015). Furthermore, children lack decision-making skills and are unable to give informed consent for themselves. Parents usually provide surrogate consent for their children with the child's "best interest" at heart, a highly contentious concept in itself. While parents are generally the best-fitted surrogate consent-givers for their children, defining a child's "best interest" is multifaceted, and there are often cases when parents make decisions that seem opposite of the best interest of their child (Botkin et al., 2015). The ethical implications surrounding the genetic testing of children necessitate further investigation.

Perhaps the most significant challenge regarding cancer panel testing is the difficulty surrounding interpretation and communication of risk results between medical personnel and patients. Panel testing yields various results: a positive result means that a known pathogenic mutation is detected, a negative result means that no genetic variant is detected, and an ambiguous result means that a variant of uncertain significance (VUS) or benign polymorphism is detected (Hiraki et al., 2014; Tavtigian et al., 2008). While both positive and negative results generally lead to relatively concise clinical decision making, an ambiguous result makes things much more complicated. According to Tavtigian et al. (2008), panel testing often finds "missense substitutions, potential splicing variants, or small in-frame insertion-deletions that are of uncertain significance" (p. 1261). In addition, testing for multiple gene mutations at a time increases the likelihood of producing a false-positive result or of detecting a VUS. The problem with an ambiguous VUS result is that there is little information regarding the effect of these less common genetic variants (Hiraki et al., 2014; Walsh et al., 2010). As a result, the data to provide accurate genetic assessments are limited, making it difficult to interpret risk and challenging to present risks to patients (Hiraki et al., 2014). A study conducted by a Familial Cancer Program in Vermont (n = 277) reviewed factors that were potential predictors of variants of uncertain significance and assessed changes in management tactics based on these factors (Hermel et al., 2016). Out of 227 patients, 67 patients had genetic variants and eight patients had multiple variants. Forty-four patients in the study had a VUS. The study found that there were no single factors such as age or personal neoplasm history that could predict variants during panel testing. Only two cases where a VUS was identified resulted in the alteration of the patients' management tactics. Overall, it was noted that little could be done about ambiguous results with today's technology (Hermel et al., 2016). The knowledge of the potential likelihood of uncovering a genetic mutation without a means to understand or prevent the mutation is an ethical quandary that must be taken into consideration. Furthermore, when conducting a panel test that searches for multiple mutations, it is possible to discover that a patient may carry multiple mutations or variants in multiple genes (Hiraki et al., 2014). Exposing new cancer risks in addition to the risks the panel test was looking for to begin with may be an unforeseen disadvantage of panel testing that must be thoroughly discussed with patients. Discovering the risk of having passed genetic mutations onto one's child is an example of an unanticipated implication of panel testing that is considered ethically unsound (Rahman & Scott, 2007).

In addition to clinical uncertainty of results, patients often struggle to understand the meaning of testing results. A study conducted by the University of Plymouth in the United Kingdom recruited 477 women at risk of breast and ovarian cancer and asked them to interpret positive, true-negative, ambiguous, and uninformative-negative results (Hanoch et al., 2014). While women were able to correctly interpret positive and negative results, they struggled to

understand the meaning of both uninformative and ambiguous results. When presented with uninformative-negative results, approximately half of the women learned nothing from the results. A substantial amount of women believed an uninformative-negative result signified a mere average probability of developing cancer. Other women believed an uninformed-negative result signified a decrease in cancer development risk. Ambiguous results yielded similar uncertainty in women's interpretations. Over half of the sample viewed the ambiguous results as uninformative, 40% saw ambiguity as an average risk of cancer, and a minority of women believed that ambiguity increased the risk of developing cancer (Hanoch et al., 2014). From these results, the study concluded that health care professionals should increase measures to ensure correct interpretation of uninformative-negative and ambiguous results for patients (Hanoch et al., 2014). However, with little ability to treat variants of uncertain significance, it is difficult for medical professionals to fully communicate risks to patients. A VUS or benign result is clinically interpreted as a negative risk, but this is not how patients interpret the result.

Beyond issues with interpreting CGT results, recent studies suggest that people who learn their genetic risk of certain cancers often do not even take any actions with their results (Rapaport, 2016). A study conducted in California analyzed survey data from 762 customers who used direct-to-consumer cancer-risk profiles to assess their cancer genetic risk. After 6 months, the study found that people who were at a higher risk of developing neoplasms were no more likely than those with an average risk to change their diet, exercise, or to seek cancer screening. The study concluded that personalized CGT will not hold any "medical crystal ball" and that they alone will not even necessarily encourage patients to take action based on their results (Rapaport, 2016).

Risk management recommendations for VUS results are based on genetic and familial risk. Myriad Genetics, a molecular diagnostic company, recommends that clinical management of VUS carriers be based upon personal and family history and not the presence or absence of the variant itself. Each report given to patients after testing includes "guideline-based medical management considerations for negative and positive patients (either of which may contain variants of uncertain significance), and information for family members" (Myriad Genetics Laboratories, 2018). Some health care providers choose to increase surveillance or pursue treatment options beyond that recommended for such variants (Plon et al., 2011). Still, there is no explicitly defined follow-up plan for VUS results. The unclear course of treatment to pursue after receiving a VUS result may bring feelings of increased anxiety for patients who undergo CGT. Challenges such as this surrounding the communication and interpretation of cancer panel testing present the potential for ethical turmoil.

Limitations in the Literature

Limitations in the extant literature on CGT are varied. Further research is needed regarding the psychosocial implications of CGT as a whole. It is becoming increasingly important to understand the impact of providing personalized risk assessments via panel testing to implement a genetic testing process that enhances both the experience of patients and the clinical utility of the testing (Hiraki et al., 2014). In addition, the growing interest in CGT may require standardized tools to fully understand and generalize the cognitive aspects of patients who undergo testing (Schlich-Bakker et al., 2006).

Many studies regarding the psychosocial implications of CGT provided the mean age of those who participated in the study. Most of the participants, both male and female, were from a wide age range, averaging around 47. This points to the importance of focusing on the influence of an individual's stage in life to understand the emotional impact of genetic testing and a potential cancer diagnosis (Schlich-Bakker et al., 2006). More specifically, studying women under the age of 45 may present different psychosocial implications because these women potentially have young children, extensive responsibilities, and the expectation for a long life (Claes et al., 2004).

In addition to focusing on young females who undergo genetic testing, more research is needed on those who receive an inconclusive test result (Schlich-Bakker et al., 2006). Much of the literature neglects to discuss the psychosocial implications of an unclear or variant of unknown significance result on patients participating in CGT (Voorwinden & Jaspers, 2016). Along these lines, future research is necessary on how genetic models predict cancer risk and to determine the frequency and predictive values of less common variants (Hiraki et al., 2014).

Common limitations in the literature surrounding CGT and the related psychosocial and ethical implications involve small or homogeneous samples (Aspinwall et al., 2011; Pasacreta, 2003), lack of studies carried out in the United States (Bennett et al., 2012; Eijzenga et al., 2014; Ho et al., 2010; Tuinman et al., 2008), and a lack of qualitative study (Aspinwall et al., 2011; Hanoch et al., 2014; Hermel et al., 2016; Pasacreta, 2003).

Conclusion

The past 20 years have seen significant improvements in the field of CGT. Genetic testing is an excellent avenue for early identification of hereditary cancer syndromes and for prompt risk management and tailored treatment. Genetic counseling provides a personalized experience for patients and has been known to reduce patients' anxiety associated with a cancer diagnosis. Both qualitative and quantitative studies have been conducted to understand the psychosocial and ethical implications of genetic

testing in regard to both patient care and clinical utility. Established literature regarding the history, role of nurses, and the psychosocial and ethical implications of CGT reveals a need for future research to fill the current gap that exists surrounding the psychosocial implications of cancer genetic panel testing, particularly with regard to incidental findings.

Further research in this area will be critical in defining the future of the nurse's role in CGT. This research will provide a pathway for nursing programs to include CGT in their curriculums and to set clearer expectations for nurses in this setting. With improved patient outcomes in mind, the practice of CGT as a whole will continue to progress with further research as nurses, and other health care professionals are made more aware of how these practices affect patients psychosocially.

Acknowledgment

The authors would like to acknowledge Elizabeth Shieh of the Knoxville Comprehensive Breast Center.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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