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ORIGINAL ARTICLE

Evolution of cancer risk assessment and counseling related to psychological, financial and legal implications

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Abstract Cancer risk assessment, genetic counseling and genetic testing have experienced advances and changes over the past two decades due to improved technology, legal movements to protect those at an increased risk for cancer due to genetics, as well as advances in detection, prevention and treatment. This brief article will provide a summary of these advances over three eras of cancer genetics: pre-discovery of the more common high impact genes, namely *BRCA1*/*BRCA2* and the mismatch repair genes associated with Lynch syndrome; the time during which the genes were being discovered; and current day.

Keywords Genetic counseling · Genetic testing · Hereditary cancer · Cancer genetics · Hereditary breast–ovarian cancer · Lynch syndrome

Pre-discovery of genes (pre 1994)

The psychological implications of being at an increased risk for cancer due to family history have evolved over the years. Before the genes were discovered family members had to rely solely on the family history of past and current generations to guide their decisions related to cancer detection and prevention. These family members would witness family member after family member develop an associated cancer due to a hereditary cancer syndrome at very young ages, typically 10–20 years earlier than the onset of sporadic cancers. Due to the devastation that struck these hereditary cancer families, many individuals would choose to undergo prophylactic surgeries based on the family history alone, most commonly prophylactic bilateral salpingo-oophorectomies at a young age. According to Lynch et al. [1], close to 20 % of high risk women underwent prophylactic oophorectomy before the *BRCA* genes were discovered and ultimately tested negative for the mutation found in their respective families. Many of these procedures were carried out due to fear and the belief that the question was not "if" they would ever develop cancer but "when" they would develop cancer as so many of their family members had already done. In this pre-discovery era many of the psychological implications for high-risk family members involved uncertainty, fear of cancer development and anxiety.

During this era most genetic testing was being done through research protocols, usually in a university setting with multiple collaborators. Some research protocols would provide genetic results based on linkage analysis studies, whereas other studies aided in the discovery of the genes without providing specific results. Since these studies were part of research studies there was typically no cost to the participants.

There was much concern by family members regarding how health care insurance providers would respond to the knowledge that an individual was at high risk for developing cancer. There were cases of insurance discrimination stating the condition was pre-existing since it was a genetic condition. Therefore, many high risk individuals were anxious and feared losing health care insurance or being prorated at a rate that was not financially feasible. Many of the screenings and preventive surgeries conducted at that time were solely based on a strong family history, and there were concerns about whether an individual's health care

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insurance policy would cover the screenings and preventive surgeries. Some laws were in place but did not provide the protection needed for high risk individuals to feel safe from discrimination.

Discovery of genes (post 1994–current day)

Once the more common, high impact genes were discovered in the mid-1990s and testing became commercially available high risk individuals had the option to undergo genetic testing to discover their actual genetic risk for developing the cancers that occurred in their families. The testing helped to reduce some of the uncertainty these individuals faced as they approached the age at which other family members had been diagnosed or succumbed to cancer. However, the ability to know one's genetic risk raised other concerns of increasing cancer worry in those individuals who tested positive. Lerman et al. [2] conducted a study looking at this very issue and found that those individuals in high risk families who chose not to undergo genetic testing or obtain their result had a higher level of anxiety compared with those who tested positive and were yet unaffected by cancer. These findings helped to clarify the benefit of genetic testing for most individuals in a hereditary cancer family.

Survivor guilt also began to psychologically impact those who tested negative, with some wondering why they were spared while others in their family were not. Wagner et al. [3] noted increased depression rates in *BRCA1/2* non-carriers attributing this increase to survivor guilt. Some of the individuals who tested negative had a difficult time transitioning their thinking from the belief that they were at inordinately high risk for cancer to accepting that they were at only the general population risk. Some would continue to have the heightened screening recommended for those at high risk, demonstrating the difficulty of believing the accuracy of a negative genetic test.

The discovery of the genes allowed clinicians to limit the frequent screening and preventive surgery to only those who were determined to be at an increased genetic risk. This helped reduce the health care burden and costs of screening, as those who tested negative could revert to the general population guidelines. "This analysis suggests that it is cost-effective to test every-one with colorectal cancer for mutations associated with the Lynch syndrome and then screen healthy first-degree relatives of persons with cancer who screen positive for the Lynch syndrome" [4]. The genetic testing also gave the opportunity for family members to know more about what the future may hold for their children. Those who tested negative for a mutation with an autosomal dominant pattern of inheritance could be assured that their children did not inherited the mutation. As wanting to know their children's risk was one of the motivating factors to undergo genetic testing, this was a great relief to many. Those who tested positive could know that each of their children had a 50 % chance of inheriting the deleterious mutation; since most hereditary cancer syndrome cancers have adult-age onset, testing was encouraged once the children reached the age of majority and so were able to provide legal consent.

Genetic testing for the hereditary cancer genes became commercially available in the mid-1990s through CLIA-approved laboratories in the United States. For families manifesting the cancers associated with hereditary breast–ovarian cancer, the testing usually ordered was *BRCA1* and *BRCA2* sequencing and, later, testing for large deletions and rearrangements within those genes. For families with cancers integral to Lynch syndrome (LS), the testing would generally be of the *MLH1*, *MSH2* and *MSH6* genes. The cost of testing the main hereditary cancer syndrome genes was $2500–4000 depending on the laboratory used for the testing. This amount was billed to insurance companies and the patient would have to pay the balance. Pre-determination of coverage was often pursued so the patient would have an idea of what would be due out of pocket. Unfortunately, the cost prohibited some from completing the testing. This not only limited that person's knowledge of their own risk to guide their cancer risk management but also prevented the identification of that family's specific mutation, inhibiting at risk unaffected relatives from learning their own carrier status. Once the mutation was found in a family then subsequent testing of the one familial mutation was $375–475 per test. In 1994 and 1995, Myriad Genetics Laboratories, Inc. was given patents on the genetic testing of the *BRCA1* and *BRCA2* genes. Costs of *BRCA1/2* testing were determined by Myriad and did not have the opportunity to be driven down by competing laboratories. In 2013 the Supreme Court overturned the patents, allowing other laboratories and research institutions to conduct *BRCA1/2* genetic testing at their set rates [5].

As genetic testing became commercially available, although somewhat expensive, the question arose as to whether health care insurance policies would cover the genetic testing and whether the request for coverage could raise a red flag regarding the individual's high risk for developing cancer. Many health insurance policies did cover the genetic testing, mostly in a group insurance plan setting, whereas private or smaller policies were more likely to have a blanket policy not to cover genetic testing. One of the federal laws put into place to help prevent health care insurance discrimination was the Kennedy–Kassebaum law, which went into effect in 1996. This bill is also known as the Health Insurance Portability and Accountability Act (HIPAA). It was first proposed with the

simple objective to assure health insurance coverage after leaving a job. This is important since many Americans have employer-based group insurance plans; the law states that if an individual changed or lost a current job then a subsequent employer could not deny that person health care insurance due to a pre-existing condition.

Litigation has occurred where health care insurance providers refused to cover prophylactic surgeries for individuals at high risk due to family history. The health care insurance company lost these cases [6] leading to a precedence of insurance coverage for prophylactic mastectomies with reconstruction and prophylactic oophorectomy, offered to all eligible high risk women.

Current day

The core psychological implications such as fear of a positive result, risk to children, etc., related to cancer risk assessment and genetic testing have not changed much since the genes were discovered. However, many advances have been made in relation to early detection, prevention and treatment over the past few decades. It is these advances that provide high risk individuals with hope for prevention and, if diagnosed, a cure. Early on in the discovery of the cancer genes, screening for *BRCA1/2* carriers included monthly self-breast exams, bi-annual clinical breast exams and annual mammograms. This current screening protocol according to the National Comprehensive Cancer Network (NCCN), v.2.2015 [7] is breast awareness starting at age 18, clinical breast exam every 6–12 months starting at age 25, between ages 25–29 annual breast MRI or mammogram if MRI is unavailable, between ages 30–75 annual mammogram and breast MRI. In relation to LS and colon cancer screening, originally flexible sigmoidoscopy was recommended, but now a full colonoscopy is recommended for mismatch repair (MMR) mutation positive individuals. According to the NCCN Guidelines [8] a baseline colonoscopy should be completed between the ages of 20–25, or 2–5 years prior to the earliest colon cancer in the family if it was diagnosed before age 25, and repeated every 1–2 years. In addition, there are recent studies with data to suggest that aspirin may decrease the risk of colon cancer in LS; however, at this time the data are not sufficiently robust to make a recommendation for its standard use [9]. These are a few of many examples of how screening recommendations have changed and become more specific and targeted for high risk individuals. Prophylactic surgeries have also evolved over time and become more defined to reduce cancer risk. Due to the fairly recent discovery that serous epithelial carcinoma of the ovary can actually start in the fallopian tubes [10, 11], it is recommended that a risk-reducing oophorectomy be completed with a bilateral salpingectomy [7]. Therefore, a risk-reducing bilateral salpingo-oophorectomy is the standard recommendation for *BRCA1/2* mutation carriers as well as LS MMR mutation carriers. In addition, surgical options for MMR positive individuals who develop a colon cancer have leaned towards a subtotal colectomy rather than a resection or hemicolectomy [12].

Targeted therapies for hereditary cancer gene carries are also developing. Currently, Parp-inhibitors are recommended for *BRCA1/2* carriers who develop ovarian cancer [13] and according to the manufacturer's protocol have failed three lines of standard treatment. Recently, anti-PD1 immunotherapy treatments have gone into clinical trials for metastatic colon cancers that are MSI high, which would include the majority of LS tumors [14, 15]. The anti-PD1 breaks the T cell-PD1 bond that occurs in cancer cells allowing the T cell to be free to attack the cancer cells. Anti-PD1 drugs have been very effective in treating melanoma [16] and lung cancer [17]. With all of these advances in detection, prevention and treatment it is hopeful that high risk individuals will have increased hope with improved outcomes.

Historically, specific cancer genes were selected for testing based upon an individual's personal family history, with testing of the most probable genes ordered. Testing would be completed in a step-wise manner starting with the highest differential diagnosis. For example, if a family history showed some characteristics of LS but did not meet classical characteristics, and it also showed some signs of attenuated familial adenomatous polyposis (AFAP) the testing would be initiated with the LS genes and if no mutation was found then a second test would be ordered for the *APC* and *MYH* genes, with a few months span of time between the testing results. A charge for each of the tests would also be incurred. In the last few years, multi-gene panels have been offered by genetic laboratories at the same cost as single or syndrome gene testing. The turnaround time for results is a bit extended to 3 weeks compared to 1–2 weeks due to the next-generation sequencing platform used by the laboratories. Utilizing a multi-gene panel offers the individual genetic testing of a targeted set of syndrome-specific genes or the complete panel of known genes related to an increased risk of cancer. Some drawbacks to this selection include genes not fully understood at this time and the discovery of a genetic mutation that wasn't even suspected, catching the individual off guard for a new set of cancer risks. Due to technological advances the cost of genetic testing has been driven down to range from $1500 to 3000, depending on the laboratory utilized. Additional cascade testing within the family will range from $200 to 375 per family member.

In 2008 a new federal law was enacted called the Genetic Information Nondiscrimination Act (GINA) [18].

GINA is an Act of Congress designed to prohibit the use of genetic information in health insurance and employment. Not only does GINA prevent discrimination in health care insurance based on genetic test results but it also prevents discrimination based on family history. In addition, employer discrimination is prohibited by this law as well. Senator Ted Kennedy called it the "first major new civil rights bill of the new century." (See: http://www.geneticfairness.org/act.html.) Federal laws such as GINA have allowed high risk individuals to seek out genetic testing to guide their health care with less anxiety of losing health care insurance.

Cancer risk assessment and counseling has definitely evolved over the years with many implications in psychological, financial and legal issues. This article has attempted to highlight some of the major advances and provides only examples of many of the advances that have occurred over the past few decades. The goal for a cure to cancer is a daunting task, but with the advances made in hereditary cancer it is hopeful that end will be reached for all cancers as time goes on.

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