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Hereditary Cancer Genetic Testing:

30 Years of Impact on Cancer Care

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Introduction

In the early 1990s Mary Claire King's group postulated the existence of a breast cancer-susceptibility gene, localized to chromosome 17.[1] In 1994 the *BRCA1* gene was discovered,[2] and its counterpart *BRCA2* would follow a year later.[3] As we celebrate 30 years since this monumental breakthrough, it is important to reflect on the impact genetic testing for hereditary cancer has had on cancer care and prevention.

Genetic testing for hereditary cancer has evolved substantially. With time we have learned that comprehensive hereditary cancer testing should include evaluation for gross genomic deletions, duplications, and large rearrangements.[3] We have learned how to evaluate the consequence of DNA alterations on the structure and function of RNA.[4] The arsenal of tools to resolve ambiguity in genetic variant interpretation continues to grow. Testing turn-around-time has been dramatically reduced thanks to laboratory automation, advances in sequencing technologies, and bioinformatics. The discovery of additional genes linked to hereditary cancer has led to a paradigm shift towards multigene hereditary cancer panels as the standard of care.[5] Today we enjoy expanded insurance eligibility criteria and increasingly patient-friendly laboratory billing practices that continue to make this testing more widely available.

The positive impact of identification and treatment of individuals with hereditary cancer predisposition cannot be overstated. Hereditary cancer genetic counseling provides personalized risk-assessment, patient education, and psychosocial counseling. Those at increased risk of cancer may be offered early detection procedures, risk-reduction measures, or personalized cancer treatment.

Genetic Counseling and Risk Assessment

When considering the benefits of genetic testing, it is easy to overlook the value of genetic counseling and personalized pre- and post-test risk assessment. The initial pre-test risk assessment is facilitated by the construction of a three-generation pedigree. Patients are often tasked with completing pre-appointment paperwork, which encourages the patient to speak with relatives, clarify details, and obtain relevant documentation such as pathology reports, consultation notes, and genetic testing reports whenever possible. Studies have shown that these pre-consultation questionaries increase accuracy in reported family history and resultant risk assessment.[6,7] Even in cases where genetic testing is not indicated, documenting an accurate family history in the medical record can help guide the continued medical care of the patient. The simple act of creating a visual representation allows a patient to envision the relatedness, provides an opportunity for education, and can serve as a motivator for compliance with recommended interventions.[8] In addition to pedigree analysis, pre-test risk assessment involves estimating the probability that a hereditary cancer predisposition will be identified in a given patient. This is accomplished by reviewing the patient's personal and family history to determine

if they fulfill criteria outlined by consensus guidelines (e.g. National Comprehensive Cancer Network: NCCN ®, United States Preventative Task Force, American Society of Breast Surgeons), and by utilizing probability assessment tools such as BayesMendel,[9] Penn II,[10] or PREMM5.[11] Defining a person's pre-test risk allows for a more informed decision about pursuing genetic testing, and can provide evidence of risk to compel insurance to cover testing.

Post-test risk assessment is just as crucial, as this process contextualizes a patient's results within their overall medical picture. Notably, post-test risk assessment is not limited to only patients whose testing identifies a causative mutation. For those with significant family histories of cancer, but uninformative genetic testing results, genetic counseling will often include an assessment of the residual lifetime risk to develop breast cancer. One of the most utilized tools for this endeavor is the Tyrer-Cuzick (TC) model.[12] The most recent iteration of this risk algorithm includes assessment of personal risk factors such as age, body mass index, menstrual history, and breast density. The evaluation also includes a nuanced three-generation family history, which includes details on both affected and unaffected relatives (illustrated by the difference in risk for someone with 1 of 1 versus 1 of 5 aunts affected with cancer). Finally, TC analysis is able to adjust its risk quantification based on genetic testing results, not just for the proband but for other relatives as well. While no risk model can determine a precise risk to develop cancer, risk tools such as the TC offer a way to communicate the reduced, but not eliminated, residual risks for patients that are gene test negative. Further, elevated risk of breast cancer through a TC or other risk model is a commonly accepted line of evidence for insurance coverage of increased breast screening measures, such as breast MRI.[13]

Cancer Prevention

Risk assessment is most fruitful when accompanied by effective tools for intervention, as illustrated by our ability to prevent cancers before they develop in those who are gene test positive. For example, bilateral salpingo-oophorectomy (BSO) is available to those at increased risk of ovarian cancer. The link between *BRCA1, BRCA2,* and ovarian cancer has been long established; a recent metanalysis demonstrates a penetrance by age 70 of 39-58% for *BRCA1* and 13-29% for *BRCA2*.[14] Similarly, the association between Lynch syndrome and ovarian cancer is well known, with an estimated penetrance of 38% by age 80 for the highest risk gene, *MSH2*.[15] More recently, the constellation of genes associated with ovarian cancer has expanded to include several moderate-risk genes, such as *BRIP1*, *RAD51C*, *RAD51D* and *PALB2*.[16,17]

While screening tools exist for ovarian cancer, such as transvaginal ultrasound or CA-125 blood tests, these measures have not demonstrated reduction in cancer mortality.[18] Comparatively, BRCA-carriers who elect a BSO see a 90% reduction in the risk to develop ovarian cancer.[19] This corresponds with both an increased overall survival and cancer-specific survival in BRCA-carriers who elect BSO.[20–22] Current NCCN guidelines recommend BSO at age 35-40 for *BRCA1* carriers, with the consideration to delay risk-reducing surgery to 40-45 in *BRCA2* carriers.[23] BSO has become the standard of care for cancer prevention in those with hereditary risk of ovarian cancer.

Despite the benefits, the choice and timing of gynecologic risk-reducing surgery are complex and informed by medical and psychological factors.[24] The risk reduction of BSO must be weighed against the increased risk of cardiovascular events, accelerated bone density loss, as well as concentration and mood difficulties of surgical menopause. Further, methods of cancer prevention continue to evolve. More recent molecular data provides compelling evidence that

many epithelial ovarian carcinomas are derived from the fallopian tube and endometrium, not the ovary itself.[25] Evidence from population-based studies demonstrate that salpingectomy imparts a 42-65% reduction in risk of ovarian cancer.[26–29] Further studies are needed to establish how this risk reduction translates to those with genetic high-risk of ovarian cancer. The promise of this early data is reflected in the most recent iteration of NCCN guidelines, which now include the discussion of upfront salpingectomy with delayed completion oophorectomy for at-risk women who are opposed to BSO in the recommended timeframe. Individuals who are interested in this alternative approach are encouraged to so as part of ongoing clinical trials evaluating this surgical decision.[23]

Early Detection

Risk-informed screening is an additional line of defense against cancers that cannot be prevented. It is well understood that population-based screening for cancers such as breast, colon, or cervical cancer provide improve outcomes and reduce cancer mortality. Tailored screening for those deemed at high-risk based on positive genetic testing has shown similar results.

One such example is high-quality colonoscopy with polypectomy. As colonoscopies can detect both early colon cancers, as well as neoplasia that is still confined to a polyp, colonoscopies straddle the line between cancer prevention and cancer screening. Hallmark studies have demonstrated that increased frequency of colonoscopies reduces the incidents of colon cancer by 62% in individuals with Lynch syndrome.[30,31] Factors such as increased hereditary risk, subtle endoscopic appearance, and rapid carcinogenesis seen in Lynch syndrome mean that not all colon cancers can be prevented through detection in the polyp stage. However, studies attribute the observed 65-72% reduction in colon cancer mortality to colonoscopies and the resulting earlier detection of colon cancers.[31,32]

For rarer hereditary cancers it is difficult to demonstrate reduced cancer mortality; instead, success may be defined as the detection of early-stage malignancy when metastatic presentation is the norm. For example, diffuse gastric cancer (DGC), a rare subtype of gastric malignancy, characterized by a carpet-like presentation along the lining of the stomach and a signet-ring cell histology. As DGC tumors do not form a discrete mass, they are difficult to detect endoscopically and typically present late stage. A single-center investigation of 120 patients with DGC revealed that 61% were stage IV at discovery, and median survival for the group was eight months from diagnosis.[33] Pathogenic alterations in the cell adhesion protein e-cadherin, encoded by the *CDH1* gene, confer a risk of 70% for males and 56% for women to develop DGC by age 80.[34] For *CDH1*-positive individuals, the dramatically increased risk of DGC coupled with the inefficacy of endoscopy screening necessitates consideration of prophylactic gastrectomy. A cohort study of 56 *CDH1*-positive families identified 17 individuals undergoing prophylactic surgery. Of these 17 specimens, occult DGC was identified in 13 or 76.5% of specimens.[35] Given that complete resection is the only potential curative approach for DGC, the consequence of early detection (in no small part due to identification of high-risk individuals through genetic testing) is clear.

Cancer Treatment

For those that develop a hereditary cancer, knowledge of genetic causation provides insight into effective therapies. For example, *BRCA1* and *BRCA2* are one of several genes that encode

proteins needed to repair DNA damage via homologous recombination. In homologous recombination, DNA damage that might otherwise cascade into tumorigenesis is instead corrected using the counterpart allele found on the homologous chromosome as a template. As homologous recombination is one of few methods for remedying double-stranded DNA breaks and collapsed replication forks, this repair pathway is essential to the integrity of the genome.

A homologous recombination deficient (HRD) phenotype is a complex genomic signature. Current methodology deems a tumor HRD when there are signs of HRD cause (for example a somatic or germline *BRCA1/2* mutation) or HRD effect (for example loss of heterozygosity, telomeric allelic imbalance and/or large-scale state transitions).[36] HRD is an important biomarker in cancer treatment as it impacts the effectiveness of PARP-inhibitor therapy. Poly ADP-ribose polymerase (PARP1) facilitates an alternative modality of DNA repair, a pathway that becomes essential for cell survival when homologous recombination is knocked-out. As early as 2005, experiments demonstrated that *BRCA1*- and *BRCA2*-deficient cell lines are highly sensitive to PARP-inhibition.[37,38] Flash forward to today, evidence of germline pathogenicity and HRD phenotype is a fundamental tool in guiding therapies for ovarian,[39] breast,[40] prostate,[41] and pancreatic cancer.[42]

Similarly, knowledge that an individual has Lynch syndrome can significantly impact cancer treatment choices. Lynch syndrome results from germline defects in the mismatch repair (MMR) mechanism. Tumors resulting from Lynch syndrome will typically exhibit a characteristic phenotype: microsatellite instability and loss of immunohistochemistry expression of one or more of the MMR proteins (MLH1, MSH2, MSH6, and PMS2). Assessment of microsatellite instability and MMR function was initially a modality used to screen tumors for Lynch syndrome[43]; now it represents a deciding factor in cancer therapy decisions. The failure of DNA repair secondary to MMR deficiency leads to an accumulation of somatic mutations. This high mutation burden within the tumor serves as a red-flag to the immune system, making MMR-deficient tumors highly sensitive to immune checkpoint blockade therapy.[44–46] Our own understanding of the mechanism of these hereditary cancers provides a targeted and effective treatment that utilizes the body's own immune defenses against the tumor.

Conclusion

The choice to undergo genetic testing for hereditary cancer predisposition is a complex one. Lack of awareness, family dynamics, fear of genetic discrimination, psychological impact, cultural beliefs, and cost remain barriers to genetic testing uptake.[47–50] That said, there are still substantial benefits. Personalized risk assessment empowers patients with knowledge of their family health history and arms them with data to promote informed decision-making. When risks are elevated, cancer prevention by way of chemoprevention, lifestyle modification and risk-reducing surgeries demonstrate improved survival. When cancer cannot be prevented, early detection can downstage tumors and improve outcomes. Even in cases where cancer is not discovered until advanced stages, knowledge of genetic causation now informs therapeutic decisions. These drugs are designed to exploit the weakness of the inherited mutation; singling-out tumor cells while leaving healthy cells unharmed.

Every day more personalized therapies, targeting not only inherited, but also acquired somatic genetic alterations, enter the market. From 2000 to late 2022, 97.4% of FDA approvals for solid tumor therapeutics were products that bind to or address a specific molecular target.[51] As we look to the future, there is potential in the form of polygenic risk scores. A polygenic risk score

uses data gleaned from genome-wide association studies to provide statistical likelihood of disease. Polygenic risk scores stand to benefit the 30% of individuals who have a familial component to cancer development who will test negative for hereditary cancer predisposition.[52] For those with a hereditary cancer syndrome, there is hope in the form of cancer vaccines. Clinical trials are actively recruiting individuals with hereditary cancer predisposition, investigating a vaccine which can trigger an immune response to prevent the formation of cancer.

We have come a long way in the 30 years since *BRCA1* was first cloned and sequenced. Years of genetic research informs personalized risk assessment for each patient. When the likelihood of cancer is elevated, there are options for prevention, early detection, and effective targeted therapies. Now more than ever, genetics plays a pivotal role in the fight against cancer. The accomplishments made and the lessons learned from hereditary cancer genetic testing illustrate the promise of precision medicine.

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