Current Indications for Consideration of Evaluation for Hereditary Cancer Predisposition Syndromes and How They Can Change Management

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ABSTRACT

Our current understanding of the genetic mechanisms that underly cancer pathogenesis is rapidly expanding. Hereditary cancer predisposition syndromes are important to recognize for diagnostic and treatment decision-making but also for family members so they will benefit from surveillance and treatment options. This brief review gives primary care and oncology caregivers a summary of the evolution of hereditary cancer predisposition syndromes, indications for consideration of testing and therapy of patients and families.

KEYWORDS: cancer, genetic, hereditary, BRCA, Lynch

BACKGROUND

Approximately 1.7 million individuals were diagnosed with cancer in the United States in 2018 and it is a leading cause of death nationwide.[1] In Rhode Island, between 1995 and 2016, there were approximately 6100 new cancer diagnoses annually.[2] According to the National Cancer Institute, some of the most common cancers diagnosed include breast cancer, prostate cancer, colon cancer, melanoma and pancreatic cancer.[1] One of the most prolific areas of cancer research involves the identification of pathogenic variants (mutations) in genes that alter the function. These gene changes can be somatic (most common) or germline. It is estimated that about 5–10% of cancers are due to hereditary predisposition. Genetic abnormalities vary with tumor type. For example 24% of ovarian cancers, 8–10% of pancreatic cancers, 12% of metastatic prostate cancers, and 17% of early onset colorectal cancers are associated with mutations.[3-6] Hereditary cancer predisposition syndromes have been associated with significantly increased lifetime risk of development of cancer and their identification is critical for patients and families.

Breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*) were the first genes to be linked to hereditary cancer syndromes. *BRCA* are correlated with early onset and/or concurrent breast and ovarian cancers. *BRCA1* and *BRCA2* genes were initially cloned in 1994.[7] In 1996, *BRCA1/2* sequencing became clinically available. Shortly thereafter, genetic testing for hereditary colon cancer (Lynch syndrome) became available. In 2010, with the introduction of next generation sequencing (NGS), significant advances have been made in gene discovery, decreasing the time required for results and making genetic testing more affordable. Today, high penetrance genes are defined as those that confer a greater than 5-fold lifetime risk of cancer in comparison with the general population risk. Moderate penetrance genes incur a 2-3-fold increased risk of cancer.

The aim of this brief review is to provide an update on the current indications and implications of germline genetic testing for hereditary predisposition syndromes and to discuss specific surveillance and therapeutic options. We will also describe how the selection of treatment based on molecular biomarkers has taken oncology to the age of precision medicine.

INDICATIONS FOR GENETIC EVALUATION FOR HEREDITARY CANCER SYNDROME

There are many different hereditary cancer predisposition syndromes. **Table 1** provides a summary of common cancer types and criteria to identify individuals at a high risk of a hereditary predisposition who might benefit from genetic evaluation and counseling.[8-9] The National Comprehensive Cancer Network (NCCN) has criteria for identification of those who are at a higher risk for hereditary breast and ovarian syndrome and Lynch syndrome.[10-11] Other tools include Chompret criteria for Li Fraumeni syndrome, the Melanoma Cancer Syndrome Assessment Tool, and *PTEN* risk calculator for *PTEN*-Hamartoma syndrome for other hereditary cancer syndromes in addition to *BRCA* and Lynch syndrome. In general, features that are concerning for a hereditary cancer predisposition syndrome include early age of onset, multiple primary tumors in one individual, cancers with high-risk qualities (such as triple negative breast cancer or medullary thyroid cancer) or multiple cancers in successive generations. Colonic polyposis can also raise concern for a hereditary predisposition. **Table 2** provides a summary of the current polyposis burden recommendations for genetic evaluation and counseling.

Advances in gene sequencing and evolving understanding of cancer susceptibility risk attributed to pathogenic variants will likely refine current genetic testing criteria. For example, germline genetic testing for pediatric cancer has demonstrated that in 8.5–14% of pediatric cases, a hereditary

Table 1. Common cancer indications and criteria that warrant genetic evaluation for hereditary cancer predisposition

Basal cell carcinoma (BCC)	> 5 BCC
	BCC diagnosed at < 30 y
Brain cancer	Family history of cancer: • Lynch syndrome related cancer* • Li Fraumeni**
	Subependymal giant cell astrocytoma
	Medulloblastoma and ≥10 adenomatous colon polyps • ≥10 adenomatous colon polyps • Findings of Neviod basal cell carcinoma syndrome***
Breast cancer (female)	Breast cancer diagnosed ≤45 y
	Triple negative breast cancer diagnosed ≤60 y
	Ashkenazi Jewish Ancestry
	Breast cancer and family history of cancer: • Ovarian cancer • Male breast cancer • Pancreatic cancer • Metastatic prostate cancer
	Breast cancer diagnosed ≤ 50 y and family history of: • Breast cancer • Prostate cancer
Breast cancer (male)	Personal history or family history of a close relative
Colorectal cancer	Colon cancer diagnosed ≤ 50 y
	Colorectal cancer with mismatch repair deficiency on tumor screening
	Two primary Lynch syndrome related cancers* in the same person
	Colon cancer diagnosis with first or second degree relative with a Lynch syndrome related cancer* diagnosed ≤ 50 y
	Colon cancer diagnosis and family history of 2 other with a Lynch syndrome related cancer*
Endometrial cancer	Endometrial cancer diagnosed ≤ 50 y
	Endometrial cancer with mismatch repair deficiency on tumor screening
	Two primary Lynch syndrome related cancers* in the same person
	Endometrial cancer with first or second degree relative with a Lynch syndrome related cancer* diagnosed < 50 y
	Endometrial cancer diagnosis family history of 2 other Lynch syndrome related cancers* regardless of age
Gastric cancer	Diffuse gastric cancer dx < 40 y
	Diffuse gastric cancer and lobular breast cancer in the same person
	Personal/family history of ≥ 2 cases of gastric cancer or lobular breast cancer (one dx < 50)
	Personal/family history of gastric cancer and 2 other Lynch syndrome related cancers at any age
Leukemia	Leukemia at <18 y with a second primary cancer
	Leukemia at <18 y with a sibling with a childhood cancer
	Leukemia and a family history of ≥2 Li Fraumeni associated cancer** (one diagnosed ≤45y)
Melanoma	≥ 3 primary melanomas in the same person
	Personal/family history ≥ 3 diagnoses of melanoma or pancreatic cancer
Ovarian cancer/fallopian tube, primary peritoneal	Personal history or family history of a close relative
Pancreatic cancer	Personal history or family history of a close relative
Prostate cancer	Metastatic prostate cancer

	High grade prostate cancer (Gleason ≥7) with one of the following:
	• Ashkenazi Jewish
	• >1 close blood relative with
	  ◦ Breast cancer diagnosed ≤50 y
	  ◦ Ovarian cancer
	  ◦ Pancreatic cancer
	• ≥2 close blood relatives with breast cancer or prostate cancer at any age

Renal cancer	Renal cancer diagnosed at ≤45 y
	Bilateral or multifocal renal cancer
	Renal cancer and a family history of renal cancer
	Renal cancer and a history of: • Skin leiomyoma, fibrofolliculoma or trichodiscomas • Pneumothorax • Pheochromocytoma/paraganglioma • Hemangioblastoma of retina, brainstem, cerebellum or spinal cord • Early onset uterine fibriods (<30 y)
Thyroid cancer	Medullary thyroid cancer
	Papillary thyroid cancer (cribriform-morular variant)

* Lynch syndrome related cancers: colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, brain (typically glioblastoma), biliary tract, small intestinal, sebaceous adenomas, sebaceous carcinoma, keratoacanthoma

** Li Fraumeni syndrome related cancers: soft tissue sarcoma, osteosarcoma, early onset breast cancer, brain cancer, colon cancer

*** Nevoid basal cell carcinoma syndrome: BCC diagnosed < 30 y, >5 BCC, macrocephaly

Table 2. Colonic polyposis burden that warrants genetic evaluation for hereditary cancer predisposition

> 10 adenomatous colon polyps
3–5 juvenile polyps
≥ 2 Peutz-Jegher polyps
≥ 5 serrated polyps proximal to the sigmoid colon (two polyps ≥ 10 mm)
≥ 20 serrated polyps of any size distributed throughout the colon

predisposition has been identified.[12-13] Additionally, the American Society of Breast Surgeons released a consensus guideline that recommends genetic testing for all patients with a new diagnosis of breast cancer.[14] This recommendation was based in part on a study which compared the yield of genetic testing for those with breast cancer who meet and fail to meet the National Cancer Center Network (NCCN) criteria for *BRCA1/2* testing.[15] Patients who met NCCN criteria for germline testing had a 9.39% yield with a large multicancer 80 gene panel. In comparison, patients who did not meet the NCCN criteria for germline testing had a 7.92% yield. Since the difference between the diagnostic yield was not statistically significant, the suggestion is to test all new diagnoses of breast cancer, which could double the number of patients with a clinically actionable result.[15]

GENETIC EVALUATION AND COUNSELING

The gold standard for identifying and testing those at risk for a hereditary cancer predisposition syndrome includes pretest and posttest counseling by professionals, such as genetic counselors, geneticists or oncologists trained in genetics. Part of the evaluation includes utilization of risk assessment tools which are moderately to highly accurate in predicting the likelihood of a germline pathogenic variant. Some examples of these include the International Breast Cancer Intervention Study (IBIS) or BRCAPRO for hereditary breast cancer, and PREMM5 for hereditary colorectal cancer. The benefits of pretest counseling includes: increased understanding of cancer risk, decreased worry about cancer, decreased anxiety, and decreased depression.[16] Face-to-face counseling is the ideal method to educate patients and families before and after testing is performed. As germline genetic testing becomes more and more specialized, the genetics experts can focus upon the most comprehensive, informative and cost-effective testing. If in-person counseling is not available, there are now alternative methods for providing advice and including video methods and telegenetics services.

GERMLINE GENETIC TESTING OPTIONS

The patient affected by cancer should be the first member of the family to be tested by a genetic panel as they are the most informative family member. If that person refuses or is unable to perform the testing, then consideration of testing family members is appropriate. Typically, a blood or saliva sample is collected. A skin biopsy may be necessary if the individual has had an allogenic stem-cell transplant or has a hematologic malignancy. Results typically take 3–4 weeks to return but a STAT panel that includes highly penetrant genes with a 1 week turnaround can be obtained for urgent therapeutic decision making.

MANAGEMENT

Depending upon the cancer predisposition syndrome identified, the lifetime risk of developing cancer does vary. High penetrance hereditary cancer genes are associated with a high lifetime risk of cancer. Some examples of genes that have been identified as high penetrance include *BRCA1*, *BRCA2*, *CDH1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *PTEN*, *TP53*, *RET,* and *STK11*. These genes are typically tumor suppressor genes and management recommendations that include surveillance and therapeutic options are tailored to the specific syndrome.

For example, functionally impaired *BRCA1* or *BRCA2* genes cannot repair double-stranded DNA breaks (the DNA repair or homologous recombination system), leading to genomic instability, accumulation of mutations, and cancer predisposition. In general, the risk for breast cancer is 45-65% by the age of 70 years for a pathogenic variant in either *BRCA1* or *BRCA2*.[17-18] Due to this risk, some women consider a risk-reducing mastectomy. Breast cancer specific mortality has been shown to be decreased by 81-100% after mastectomy.[19] Options for *BRCA1* and *BRCA2* management for women include: clinical breast examination every 6 months starting at the age of 25 years, increased breast screening starting at age 25 years with annual breast MRI and at the age of 30 years addition of a mammogram with consideration of tomography staggered every 6 months from the MRI. Individuals with a *BRCA* pathogenic variant or likely pathogenic variant also have the option of a risk-reducing mastectomy and salpingo-oopherectomy.[10] These can be considered after completion of child bearing. There are also specific recommendations for men carrying *BRCA1* or *BRCA2* pathogenic variants as well, including self and clinical exam starting at age 35 years and consideration of prostate cancer screening starting at age 45 years.[10] Currently there are no specific recommendations for women or men regarding increased melanoma or pancreatic cancer screening but this can be individualized.[10]

The overall goal of precision medicine is to utilize molecular changes to individualize care and choose therapies that are more effective and have fewer side effects. Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as effective agents for the treatment of *BRCA*-mutated tumors. PARP inhibitors repress a salvage gene repair system in *BRCA*

deficient cancers, leading to irreparable DNA damage in these tumor cells and tumor cell death.[20] Three PARP inhibitors were approved in the maintenance or sequential treatment of relapsed epithelial ovarian with or without *BRCA* mutations. Recently, Phase III studies of metastatic *BRCA*-mutated triple negative breast (OLYMPIAD), pancreatic (POLO) and castrate resistant prostate cancers (PROfound) have demonstrated clinically significant improvements in delaying symptomatic or radiologic progression of tumors.[21-23]

Moderate penetrance hereditary cancer genes are associated with a moderate lifetime risk of cancer. Some examples of genes that have been identified as moderate penetrance include: *ATM*, *BARD1*, *CDKN2A*, *CHEK2*, and *RAD51D*. These genes are also typically involved in the DNA repair or homologous recombination aspects of cell function. Recommendations are tailored to the specific pathogenic variant as it may implicate distinct natural history. For example, recommendations for *ATM* and *CHEK2* currently include increased screening starting at age 40 years, annual mammogram with consideration of tomography, and breast MRI staggered 6 months from the mammogram. For these two genes there are currently no surgical recommendations (for breast or ovarian cancer risk). There are also some moderate penetrance genes that do have prophylactic surgical options. *RAD51D* is associated with ovarian cancer and the NCCN currently recommends consideration of risk reducing salpingo-oopherectomy at age 45–50.[10]

FAMILY MEMBER RISK

Identification of a hereditary cancer predisposition can affect patient management, but it is also of critical importance for family members. Once a pathogenic variant or likely pathogenic variant has been identified in an individual, typically his/her first-degree relatives should be offered the opportunity to consider testing. Exceptions to this rule include minors, who, unless the hereditary cancer predisposition syndrome includes childhood onset cancers and screening (such as *TP53* and Familial Adenomatosis Polyposis), should hold off on testing until they reach adulthood and can make their own informed decision.[24] If a first-degree relative refuses testing or is unavailable, second-degree relatives can consider testing. An important implication of testing a family member who is unaffected by cancer is insurance discrimination. In the United States, citizen protection from health insurance discrimination is enforced by the genetic information nondiscrimination act (GINA). However, life insurance, disability insurance and long-term care insurance are entities exempted from GINA.

VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

Typically, when completing genetic testing, pretest counseling includes discussion of three possible results. A positive result is described as a finding of inherited a pathogenic or likely pathogenic variant in a hereditary cancer predisposition gene. A negative result is a finding of no detected gene alterations. In this situation the origin of cancer is most likely somatic and may be secondary to environmental or multifactorial causes. The third possibility is the finding of a variant of uncertain significance. This is a gene alteration that has not been reported in the literature before or does not have enough evidence to classify it as pathogenic or benign. Therefore, it is non-diagnostic. The recommendation is to update patients (especially with consistent family history of cancers) of the pathogenicity of the VUS as the scientific evidence accumulates. Family testing is sometimes helpful to sort out the significance of the result to learn if it tracks with other family members with disease. Otherwise, family testing is not recommended for their clinical management.

SOMATIC TESTING

Somatic testing, or tumor testing, has been increasingly utilized in oncology. Tumor testing often identifies multiple pathogenic/likely pathogenic variants that have evolved in the cancer and may be potential targets for treatment. Sometimes a change is identified on somatic testing that is concerning for a germline change. It is important to note that germline testing should be considered based on the patient's clinical and family history, not solely on somatic testing.

CONCLUSIONS

The field of cancer genetics and the testing techniques are quickly evolving. Some of the available panels can now test up to 100 genes. This has important implications for patients with cancer since patient and family diagnostic and therapeutic plans may be impacted.

In Rhode Island, there are multiple institutions that provide genetic services which can be utilized when there is a patient who presents with a personal or family history suggesting a hereditary predisposition. This gives the individual and their family members the opportunity to personalize their management (precision medicine), complete earlier/increased surveillance and/or consider prophylactic therapies to reduce their risk of developing cancer or improve outcomes.

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