Review

Genetic Counseling and Testing for Common Hereditary Breast Cancer Syndromes

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Throughout the past 15 years, the identification of several genes associated with hereditary breast cancer has fueled the growth of clinical genetic counseling and testing services. In addition, increased knowledge of the genetic and molecular pathways of the known hereditary breast cancer genes, as well as an increased understanding of the impact of testing on individuals has added to the ability to identify, manage, and provide psychosocial support for mutation carriers. This review provides an overview of the clinical features, cancer risks, causative genes, and management for hereditary breast and ovarian cancer syndrome, Cowden syndrome, and Li-Fraumeni syndrome. This article summarizes the genetic counseling process and genetic test result interpretation, including a review of the key elements involved in the provision of risk assessment and informed consent, as well as a review of the risks, benefits, and limitations of cancer susceptibility genetic testing. (*J Mol Diagn* 2008, 10:383–395; DOI: 10.2353/jmoldx.2008.070161)

Breast cancer affects one in eight women in the United States¹ and is caused by an accumulation of mutations in genes that promote cell growth or maintain DNA integrity.^{2,3} The majority of breast cancer diagnoses are attributable to acquired somatic mutations; however, ~5 to 10% of all cases are caused by a mutation in a highly penetrant cancer predisposition gene. Individuals who carry a mutation in a cancer susceptibility gene have a significantly higher risk to develop breast cancer, as well as other cancers, depending on which gene is mutated. The ability to identify

individuals with a hereditary predisposition for cancer provides the opportunity to educate the individual about personal and familial risk, and provide appropriate medical management.

Hereditary Breast Cancer Syndromes

Three of the most clearly described hereditary breast cancer syndromes are hereditary breast and ovarian cancer syndrome, Cowden syndrome, and Li-Fraumeni syndrome (LFS). All of these conditions are inherited in an autosomal dominant pattern, and are associated with other cancers and clinical features. Genetic testing for each of the genes associated with these syndromes is available through commercial and research laboratories, allowing health care providers the ability to offer clinical cancer genetic counseling and testing services to at-risk individuals.

Hereditary Breast and Ovarian Cancer Syndrome (BRCA1 and BRCA2)

Hereditary breast and ovarian cancer syndrome is associated with a significantly increased risk for breast cancer and ovarian cancer compared to the general population risk. Hereditary breast and ovarian cancer syndrome is caused by mutations in the *BRCA1* and *BRCA2* genes and is believed to account for the majority of hereditary

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breast and ovarian cancers.^{4–6} Women with mutations in the *BRCA1* or *BRCA2* genes are estimated to have a 60 to 80% lifetime risk for breast cancer.^{7–9} A recent meta-analysis published by Chen and Parmigiani¹⁰ found a cumulative breast cancer risk to age 70 years to be 57% and 49% for *BRCA1* and *BRCA2* carriers, respectively. An earlier meta-analysis published by Antoniou and colleagues,⁷ found an average cumulative breast cancer risk in *BRCA1* carriers by age 70 years of 65% and a 45% risk of breast cancer in *BRCA1* carriers. Several studies have also indicated that women with *BRCA* mutations who have had breast cancer, have an ~35 to 43% lifetime risk, with some studies estimating up to a 64% lifetime risk, or a 3% risk per year, for developing a contralateral breast cancer.^{8,11–15} According to an early study, 57% of *BRCA1* carriers are diagnosed with breast cancer under the age of 50, compared with 28% of *BRCA2* carriers.⁶ Men with *BRCA2* mutations are estimated to have a 6% lifetime risk for breast cancer.^{16,17} Although breast cancer in men with *BRCA1* mutations has been reported, the lifetime risk for male breast cancer associated with *BRCA1* mutations is not well defined.^{15,18–20} A recent retrospective study by Tai and colleagues,²¹ estimate that male *BRCA1* mutation carriers had a 1.2% risk for breast cancer by age 70 years.

Women who have a *BRCA1* mutation have a 15 to 60% lifetime risk for ovarian cancer; and women with *BRCA2* mutations have an estimated 10 to 27% cumulative risk.^{7–10,22} Chan and Parmigiani's meta-analysis found a 40% and 18% cumulative risk for ovarian cancer by age 70 years in *BRCA1* and *BRCA2* carriers, respectively. In addition, women with *BRCA2* mutations tend to develop ovarian cancer at an older age (after age 50) compared to those with *BRCA1* mutations.^{10,22}

Men and women with hereditary breast and ovarian cancer syndrome are also at risk for additional cancers. Several studies have found an association with *BRCA* mutations and increased risks for melanoma and cancers of the prostate and pancreas.^{17,23,24} The Breast Cancer Linkage Consortium found an increased risk for prostate cancer in *BRCA1* mutation carriers who were younger than 65 years of age [relative risk (RR) = 1.82, 95% confidence interval (CI) = 1.01 to 3.29], but not in men 65 years or older.²³ Other studies looking specifically at male *BRCA1* carriers have found a twofold to threefold increased risk for prostate cancer.^{8,23} The Breast Cancer Linkage Consortium identified a 4.65 relative risk for prostate cancer in male *BRCA2* mutation carriers, corresponding to a 7.5% cumulative risk by age 70 years.²⁵ Other studies have found a 19 to 39% risk of prostate cancer in *BRCA2* carriers.^{18,25} Increased risk for pancreatic cancer in *BRCA2* mutation carriers is well documented. The Breast Cancer Linkage Consortium data found a statistically significant increased risk for pancreatic cancer (RR = 3.51, 95% CI = 1.87 to 6.58), giving a cumulative risk by age 80 years of 3.2% for men and a 2.3% risk for women.²⁵ Another study estimated a 7% risk of pancreatic cancer before age 75 years in Ashkenazi Jewish carriers of the 6174delT mutation in the *BRCA2* gene.²⁶ The risk for pancreatic cancer in *BRCA1* mutation carriers is not as well established, although the Breast Cancer Linkage Consortium data suggests a rel-

ative risk of 2.25 (95% CI = 1.26 to 4.06) for pancreatic cancer in *BRCA1* mutation carriers.²³

Clinicopathological features of the breast and ovarian tumors in the *BRCA* spectrum are slowly emerging. *BRCA1* breast cancers tend to be more frequently negative for estrogen receptor, progesterone receptor, and HER-2/Neu overexpression when compared with presumably nonhereditary breast cancers.^{27–29} *BRCA1* breast tumors have also been found to be more frequently poorly differentiated.³⁰ Invasive ductal carcinoma is the most common histological type identified in *BRCA1* breast tumors, but there is also a higher incidence of medullary carcinoma when compared to *BRCA2* breast cancers and non-*BRCA1/BRCA2* breast tumors (13% versus 3% and 2%, respectively).²⁸ Unlike *BRCA1*-associated breast cancers, there is a less distinct pathological phenotype for *BRCA2* breast cancers. *BRCA2*-associated breast cancers tend to be higher-grade tumors than sporadic breast cancers, but the association is not as strong as with *BRCA1* breast cancers.^{27,28,31} The distribution of estrogen and progesterone receptor status in *BRCA2* breast cancers is similar to that in sporadic cases.^{27,31} In regards to HER-2/Neu status of *BRCA2*-related cancers, one study found that HER-2 overexpression was similar to that in *BRCA1* tumors, although it was not significantly different from control cases.²⁷ However, another study found lack of HER2-Neu amplification or overexpression in 18 *BRCA2* breast tumors, which was statistically different when compared to breast tumors from non-*BRCA2*-positive individuals.³²

There have been several studies that have looked at the pathological features of ovarian tumors from *BRCA1* and *BRCA2* carriers. Most of these studies have found that *BRCA1*- and *BRCA2*-associated ovarian cancers are primarily high-grade, advanced stage, serous tumors.^{33–36} Endometrioid histology is the next most common ovarian tumor pathology associated with *BRCA*-positive status.³⁷ Mucinous ovarian tumors occur at a much lower frequency in *BRCA* carriers when compared to noncarriers.^{36,37} Borderline ovarian tumors have also been identified in *BRCA* carriers, although they also occur at a frequency lower than control populations.^{37,38}

Family history is essential to clinically identifying individuals at risk for mutations in the *BRCA* genes. Hallmark characteristics include individuals who have a personal or family history of premenopausal breast cancer, multiple family members diagnosed with breast and/or ovarian cancer, multiple generations affected, the occurrence of male breast cancer, and descent from a population with high incidence of founder mutations, such as Eastern European (Ashkenazi) Jewish ancestry or Icelandic ancestry. Individuals who are identified as having a high likelihood of hereditary breast and ovarian cancer syndrome should be offered the option of genetic analysis of the *BRCA* genes.

BRCA1, located on 17q11,³⁹ encodes a 1863-amino acid polypeptide. In contrast, *BRCA2*, on 13q12-q13, is larger than *BRCA1*, encoding 3418 amino acids.^{39–42} Both *BRCA1* and *BRCA2* are tumor suppressor genes involved in DNA repair.⁴³ *BRCA1* has also been implicated in cell-cycle regulation, protein ubiquitylation, and chromatin remodeling.⁴² Mutations in *BRCA1* and *BRCA2* can occur anywhere

along the genes. However, there are three well-known founder mutations that occur at a higher frequency in the Ashkenazi Jewish population (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*).⁴⁴ Additional founder mutations have been described in Icelandics,^{45,46} French Canadians,^{47,48} Dutch,^{49,50} and African Americans, among other populations.^{51,52} The majority of deleterious mutations identified to date are frameshift or nonsense mutations or large genomic deletions or duplications.^{53,54}

Clinical management of *BRCA1* and *BRCA2* mutation carriers focuses primarily on breast and ovarian cancer risk. For breast cancer risk, it is recommended that women with *BRCA* mutations begin monthly breast self-examinations at 18 years of age and twice per year clinical breast examinations beginning at age 25.^{55,56} Annual mammography should begin at age 25 years, or 10 years earlier than the earliest breast cancer diagnosis in the family.⁵⁶ In addition to annual mammography, the American Cancer Society recently published guidelines recommending that *BRCA* carriers and first-degree relatives of *BRCA* carriers who do not know their own mutation status, also undergo annual breast magnetic resonance imaging screening.⁵⁷ Although, the evidence supporting the efficacy of tamoxifen as a chemopreventive agent in *BRCA* carriers is limited, chemoprevention using tamoxifen, a selective estrogen receptor modulator, is also available to unaffected female *BRCA* carriers. Narod and colleagues⁵⁸ found a 50% risk reduction for a contralateral breast cancer in affected *BRCA1* and *BRCA2* mutation-positive women who took tamoxifen, as did Gronwald and his colleagues.⁵⁹ Risk-reducing mastectomy is appropriate on a case-by-case basis because several studies have shown a 90% reduction (or up to a 95% risk reduction when the woman also has a concurrent or prior bilateral prophylactic mastectomy) in breast cancer risk in women with *BRCA1/2* mutations who underwent bilateral prophylactic oophorectomy.^{60–62} Discussion of the benefits, limitations, and risks of mastectomy should include a thorough review of the degree of protection, reconstruction options, follow-up management recommendations, and potential psychological impact.

In women with *BRCA* mutations, risk-reducing salpingo-oophorectomy, ideally between the ages of 35 or 40 years, or on completion of child bearing, is recommended for ovarian cancer management. Several studies, both prospective and retrospective, have found an 80 to 96% ovarian cancer risk reduction with risk-reducing salpingo-oophorectomy.^{63–66} Risk-reducing salpingo-oophorectomy has also been shown to reduce the risk by up to 56% and 46%, respectively, for developing breast cancer when performed in premenopausal *BRCA1* and *BRCA2* mutation carriers.⁶⁷

Although the role of ovarian cancer surveillance has not been shown to lead to early detection or reduce mortality, for those individuals who do not elect prophylactic surgeries, concurrent transvaginal ultrasound, CA-125, and pelvic examination should be performed every 6 months beginning at 35 years of age, or 10 years earlier than the first ovarian cancer diagnosis in the family.^{55,56} In regards to chemoprevention, long term use of oral contraceptives has been shown to reduce the risk for ovarian cancer in women with *BRCA* mutations,^{68–71} with a study by Narod and col-

leagues⁷⁰ finding that the risk of developing ovarian carcinoma decreased 20% and 60% when used for up to 3 years or used for 6 or more years, respectively.

For male *BRCA* mutation carriers, monthly breast self-examination, annual clinical breast examinations, and work-up of any suspicious breast lesions is warranted. The National Comprehensive Cancer Network guidelines also recommend that baseline mammogram be considered, with an annual mammogram if gynecomastia or parenchymal/glandular breast density is identified on baseline study.⁵⁶ Some professionals have suggested that male *BRCA* carriers should begin prostate cancer surveillance at 40 years of age, rather than age 50 years.¹⁷ The National Comprehensive Cancer Network guidelines recommend that male *BRCA* mutation carriers should begin prostate screening with a digital rectal examination and PSA beginning at age 50, or earlier, based on the youngest age of diagnosis in the family.

Cowden Syndrome (*PTEN*)

Cowden syndrome, also known as multiple hamartoma syndrome, is characterized by the formation of multiple hamartomas that may develop in any organ, as well as an increase risk for carcinoma.⁷² Facial trichilemmomas, acral keratoses, and oral papillomatous papules are pathognomonic features.^{73,74} Greater than 90% of individuals with Cowden syndrome have been found to have mucocutaneous lesions.⁷⁵ Women with Cowden syndrome have a 67 to 76% risk for benign breast disease, such as fibroadenomas and fibrocystic breast disease, and a 25 to 50% lifetime risk for breast cancer.^{72,76–78} Males with Cowden syndrome have also been described with breast cancer; however, a specific risk for male breast cancer has not been delineated.^{77,79}

The lifetime risk for nonmedullary thyroid cancer, typically follicular and occasionally papillary, is ~10%.⁷⁵ Benign thyroid disease, including multinodular goiter and adenomas are also more prevalent.⁷² Women have an increased risk for endometrial cancer (5 to 10% estimated life time risk) and uterine fibroids.^{73,75} Lhermitte-Duclos disease, or dysplastic gangliocytoma of the cerebellum, is believed to be a major component of Cowden syndrome, but the incidence of this finding in Cowden's patients is, as yet, not known.^{75,80,81} Additionally, renal cell carcinoma has been added to the operational diagnostic criteria for Cowden syndrome; however, the risk for developing this lesion has not been well defined.⁷³

Two studies by Schrager and colleagues^{82,83} studying the clinicopathological features of breast cancers associated with germline mutations in the *PTEN* gene found the usual spectrum of pathology, with infiltrating ductal cancer being the predominant invasive breast cancer. However, these two studies also identified a large spectrum of benign breast disease, including apocrine metaplasia, fibroadenomas, microcysts, adenosis, and hamartoma-like lesions with densely hyalinized collagen.^{82,83} This breast disease was reported to be bilateral and extensive.

Clinical diagnosis of Cowden syndrome is currently based on the operational criteria first developed by the

Table 1. International Cowden Syndrome Consortium Operational Criteria for Diagnosis of Cowden Syndrome

Pathognomonic criteria (mucocutaneous lesions)
Facial trichilemmomas
Acral keratoses
Papillomatous papules
Mucosal lesions
Major criteria
Breast cancer
Nonmedullary thyroid carcinoma, especially follicular thyroid cancer
Macrocephaly (occipital frontal circumference $\geq 95\%$)
Endometrial carcinoma
Lhermitte-duclos disease
Minor criteria
Other thyroid disease (eg, multinodular goiter or adenoma)
Mental retardation (IQ ≤ 75)
Gastrointestinal hamartomas
Fibrocystic breast disease
Lipomas
Fibromas
Genito-urinary tumors (eg, renal cell carcinoma)
Genito-urinary malformations
Uterine fibroids
Operational diagnosis in an individual, any single pathognomonic criterion, but
1. Mucocutaneous lesions alone if there are:
a. Six or more facial papules, three or more of which must be trichilemmoma, or
b. Cutaneous facial papules and oral mucosal papillomatous, or
c. Oral mucosal papillomatosis and acral keratoses, or
d. Six or more palmoplantar keratoses
2. Two major criteria, but one must include macrocephaly or LDD
3. One major and three minor criteria, or
4. Four minor criteria
Operational diagnosis in a family member with a known diagnosis of Cowden syndrome in the family
5. A pathognomonic criterion
6. Any one major criterion with or without a minor criteria
7. Two minor criteria

See Eng.⁷³

International Cowden Consortium in 1995 and adopted by the National Comprehensive Cancer Network Genetics/High Risk Cancer Surveillance Panel.⁵⁶ According to these operational criteria, to be diagnosed with Cowden syndrome an individual must exhibit a certain number of major or minor criteria.^{56,73} These criteria are summarized in Table 1. Approximately 80% of individuals who meet these strict operational diagnostic criteria have an identifiable *PTEN* mutation.^{73,84,85}

PTEN, a tumor suppressor gene located on chromosome 10, encodes a 403-amino acid dual specificity phosphatase with lipid and protein substrates.^{86–88} The *PTEN* protein plays a role in numerous molecular pathways involving cell cycle arrest and/or apoptosis.^{89,90} Mutations in the *PTEN* gene are also associated with Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome. These diseases, along with Cowden syndrome, comprise what is referred to as the *PTEN* hamartoma tumor syndrome.^{89,91,92}

Women who have Cowden syndrome should perform monthly breast self-examinations beginning at 18 years of age. They also require semiannual clinical breast ex-

aminations beginning at age 25 years (or 10 years earlier than the earliest breast cancer diagnosis in the family). Although it is possible that the underlying fibroadenomas and fibrocystic breast disease seen in women with Cowden syndrome may impair the sensitivity of breast imaging, expert opinion recommends that imaging with annual mammography begin around age 30 to 35 years, or 5 to 10 years earlier than the earliest breast cancer diagnosis in the family.^{56,75} As with *BRCA* carriers, the American Cancer Society recommends annual breast magnetic resonance imaging screening for individuals with Cowden syndrome and their first-degree relatives.⁵⁷ Risk-reducing mastectomy is an individual choice and should be discussed on a case-by-case basis with each patient. Although recommendations regarding breast cancer surveillance in males have not been published, if a male with Cowden syndrome develops any palpable breast lesions, it would be prudent to perform a diagnostic evaluation for breast cancer. Endometrial carcinoma screening with blind endometrial aspirations should be performed annually in premenopausal females starting at age 35 to 40 years (or 5 years before the earliest endometrial cancer diagnosis in the family), and annual endometrial ultrasonography in postmenopausal women.⁵⁶

Both men and women with Cowden syndrome should obtain a baseline thyroid ultrasound at 18 years of age, and an annual thyroid examination thereafter.^{56,75} An annual urinalysis, with consideration to annual urine cytology and renal ultrasound, should be performed in both men and women if there is a family history of renal carcinoma.^{56,75} Additionally, men and women should undergo annual physical examinations beginning at 18 years of age, and a yearly dermatological evaluation may be justified.⁷⁵

LFS (*TP53* and *CHEK2*)

LFS is a rare cancer predisposition syndrome estimated to account for ~1% of hereditary breast cancer.⁹³ LFS is characterized by early-onset breast cancer, soft-tissue sarcomas, osteosarcomas, leukemias, brain tumors, and adrenocortical tumors.^{94–98} In families with LFS, soft-tissue sarcomas, brain tumors, and adrenocortical carcinomas are known to present in early childhood.⁹⁵ Additionally, cancer of the lung, stomach, ovary, colon, pancreas, melanoma, and even Wilms' tumor, among other cancers, have been reported in Li-Fraumeni families.^{98–101}

Several studies have attempted to delineate the cancer risk associated with LFS. A study of LFS relatives in 159 extended families found that the risk for developing cancer among carriers was 12%, 35%, 52%, and 80% by 20, 30, 40, and 50 years of age, respectively.¹⁰² Another study found a 50% risk for cancer by age 40 and a 90% risk by age 60.¹⁰³ The risk for developing multiple primary cancers is also increased in LFS individuals; one study¹⁰⁴ Additionally, after adjusting for gender-specific cancers, the cancer risk between the sexes is still significantly different, with LFS females having a greater risk of developing cancer (nearly 100%) than males (73%).^{102,105} In regards to breast cancer risk, a woman with LFS has a breast cancer risk of 56% by age 45 and greater than

Table 2. Criteria for Li-Fraumeni Syndrome

Classic Li-Fraumeni syndrome ⁹⁴
<ul style="list-style-type: none"> ● Proband with sarcoma diagnosed ≤45 years, and ● First-degree relative with any cancer diagnosed ≤45 years, and ● Another first- or second-degree relative in the same lineage diagnosed ≤45 years with any cancer or a sarcoma at any age
Li-Fraumeni-like syndrome (Birch et al ¹⁰⁷)
<ul style="list-style-type: none"> ● Proband with any childhood cancer, sarcoma, brain tumor, or adrenocortical tumor diagnosed ≤45 years, and ● A first- or second-degree relative with a typical Li-Fraumeni syndrome cancer (breast cancer, sarcoma, brain tumor, adrenocortical tumor, or leukemia) at any age, and ● A first- or second-degree relative with any cancer younger than the age of 60 years
Li Fraumeni-like syndrome (Eeles ¹⁰⁸)
<ul style="list-style-type: none"> ● Two first- or second-degree relatives with LFS-related tumor (sarcoma, breast cancer, brain tumor, adrenal cortical tumor, or acute leukemia) diagnosed at any age
Chompret criteria ¹⁰⁹
<ul style="list-style-type: none"> ● One first- or second-degree relative with cancer diagnosed before the age of 46 ● Multiple primary tumors in the proband, regardless of family history

90% by age 60, with most diagnoses of breast cancer occurring under the age of 40.^{101,105,106}

Li and Fraumeni and colleagues⁹⁴ developed the first clinical diagnostic criteria for LFS, based on their study of 24 LFS kindreds, and this criteria has come to be known as the classic or strictest diagnostic criteria (Table 2). In an attempt to determine who to test for germline mutations associated with LFS, other groups loosened Li and Fraumeni and colleagues⁹⁴ strict criteria, developing criterion for Li-Fraumeni-like (LFL) syndrome. LFL, as described by Birch and colleagues,¹⁰⁷ is a proband with any childhood cancer or sarcoma, brain cancer, or adrenocortical carcinoma diagnosed by age 45, who has a first-degree or second-degree relative with a typical LFS cancer at any age, and another first-degree or second-degree family member with cancer diagnosed before the age of 60. Another definition for LFL, published a year after Birch's definition, is even less strict, as illustrated in Table 2.¹⁰⁸ More recently, Chompret and colleagues¹⁰⁹ in 2001 recommended that genetic testing for *TP53* mutations should be considered in families who meet the following criteria: a proband affected by a sarcoma, brain tumor, breast cancer, or adrenocortical cancer before age 36 years of age, with at least one first- or second-degree relative with cancer (other than breast cancer if the proband has breast cancer) before age 46 years of age, or, a relative with multiple primary tumors at any age.

Mutations in *TP53* are the primary cause of LFS.^{97,107,110,111} The *TP53* gene is a well-known tumor suppressor gene, located on chromosome 17p13.1. Dubbed the "guardian of the genome," *TP53* is associated with cell-cycle control and apoptosis.^{112,113} The *TP53* gene has one noncoding and 10 coding regions with five highly conserved domains.¹¹⁴ The core DNA-binding areas are found in domains II to IV, and domain I is responsible for transacti-

vation properties.¹¹⁵ The majority (70 to 80%) of the mutations identified in the *TP53* gene are located in exons 5 through 8.^{111,116,117} In families who meet the classical LFS diagnostic criteria, 50 to 70% have an identifiable *TP53* mutation.^{107,109,115,116,118} In families who do not meet the strict diagnostic criteria, the likelihood of identifying a *TP53* mutation is lower.^{107,109,115,118} Specifically, using the Birch and the Eeles LFL criteria, the mutation detection rate is estimated to be 21 to 40% and 8%, respectively.^{111,119,120} Using Chompret and colleagues criteria,¹⁰⁹ mutations in *TP53* will be identified 20% of the time.¹⁰⁹

Germline mutations in *CHEK2* have also been attributed to several families with classic LFS and Li-Fraumeni-like syndrome.^{120–124} *CHEK2*, located on chromosome 22q12.2, codes for a serine/threonine protein kinase, which phosphorylates p53, leading to cessation of mitosis and allowing DNA repair.¹²⁵ The *CHEK2* protein also binds to and regulates the *BRCA1* gene product.¹²⁶ It is believed, therefore, that germline *CHEK2* mutations disrupt a cell cycle checkpoint impairing the cell's ability to stop mitosis and repair DNA damage.^{122,123} Two mutations, the 1100delC mutation, a frameshift mutation that results in a premature stop codon, and R145W have both been identified in LFS families.^{121–123} However, one study assessed 15 individuals who met the LFS or LFL criteria and had tested negative for deleterious mutations in the *TP53* gene; all were negative for the *CHEK2* 1100delC mutation,¹²⁷ suggesting that this mutation is not thought to play a significant role in LFS.

Management of individuals at-risk for LFS, or with a known germline mutation, is difficult because of the diverse array of tumors associated with the condition, as well as the paucity of proven ways to detect tumors early. Current guidelines suggest that women begin monthly breast self-examinations beginning at age 18 years and semiannual clinical breast examinations starting at 20 to 25 years of age (or 5 to 10 years before the earliest breast cancer diagnosis in the family).⁵⁶ Given the evidence that ionizing radiation increases the risk of cancer in LFS carriers,^{104,128,129} there has been concern raised about the use of mammography as a breast cancer screening tool.^{104,115,129} However, current recommendations call for annual mammography and breast magnetic resonance imaging beginning at age 20 years, or earlier depending on the youngest breast cancer diagnosis in the family.^{56,57,115} Options for risk-reducing mastectomy should be discussed because some women with LFS may elect to pursue this procedure. Annual clinical evaluation is recommended, including careful dermatological and neurological examinations.^{56,115} Varley and colleagues¹¹⁵ also recommend an annual abdominal ultrasound and full blood count for children with LFS. Selective organ-targeted screening, based on individual family histories may be warranted, such as brain magnetic resonance imaging for those families with a history of brain tumors,^{56,115} although there is no published data supporting the efficacy of this approach. Additionally, the National Comprehensive Cancer Network guidelines recommend considering a colonoscopy every 2 to 5 years.

Genetic Counseling and Testing

The process of genetic counseling facilitates informed, personally-driven, decision-making, which is integral to cancer susceptibility gene testing. The purpose of genetic counseling in the oncology setting is to allow individuals an opportunity to learn how heredity contributes to cancer risk, understand their personal risk of developing cancer, understand their options for managing their cancer risk, choose a course of action that is appropriate for them, and provide them with additional resources.^{130,131} The health care professionals who provide cancer risk assessment and genetic counseling must be well prepared to meet the needs of their clients. The ability to obtain and interpret family histories, provide personalized risk assessments, educate individuals about basic concepts in cancer susceptibility, facilitate client decision-making, discuss potential medical management recommendations, and address psychosocial concerns are necessary skills for health care professionals who provide cancer genetic counseling services.¹³¹ In addition, it is critical that health care professionals who are providing cancer genetic testing services be prepared to facilitate the dissemination of genetic testing information to family members because this is integral to identifying and managing at-risk individuals.

Family History

The key to identifying individuals who will benefit from genetic testing for hereditary cancer susceptibility genes lies in the risk assessment process. The first step in this process is to obtain and analyze a complete and accurate family history. Pedigrees should include detailed medical, health, and psychosocial history on the client (proband), as well as their first-, second-, and, if possible, third-degree maternal and paternal relatives (ie, children, parents, siblings, grandparents, aunts/uncles, and first cousins).¹³² Pedigrees should also include the type of cancer, age at diagnosis, and age at death for each affected individual related to the proband, as well as information about family members unaffected by cancer.¹³⁰ Inquiries must include both maternal and paternal histories to determine from which side of the family the inherited susceptibility is being transmitted. Additionally, it is necessary to know the client's ancestry/ethnicity because some cancer susceptibility mutations have a higher prevalence in select populations.

Errors in family history reporting are well documented in the medical literature; therefore, accurate cancer risk assessment often requires confirmation of diagnosis through review of medical records or death certificates in some family members.^{133–135} In addition, family history is not static and should be updated on a regular basis because new diagnoses of cancer cases in families may alter genetic risk assessment.¹³⁶ Physical examinations of family members may also assist in the identification of cancer susceptibility syndromes, such as Cowden syndrome.

Education and Risk Assessment

Analysis and interpretation of family history allows for personalized risk assessment. Several different risk estimates, such as the risk for developing cancer or the likelihood of a genetic mutation in the family, may be provided to an individual during the counseling process.¹³⁰ Risk models calculating the likelihood of developing breast cancer use several different factors. The model of Gail and colleagues¹³⁷ estimates breast cancer risk by taking into account a woman's age at menarche, age at first live birth, number of first-degree relatives with breast cancer, and previous biopsies, with specific focus on whether there was presence of atypical hyperplasia. The model of Gail and colleagues¹³⁷ will underestimate the risk of developing breast cancer if a woman is a carrier of a cancer susceptibility gene mutation and if the woman has a paternal history of cancer. Thus, in the context of cancer genetic risk assessment, the model of Gail and colleagues¹³⁷ is more often used to provide breast cancer risk estimates to individuals who do not have family histories suggestive of a hereditary breast cancer syndrome or who have tested negative for a known familial mutation. The model of Gail and colleagues¹³⁷ is also used to counsel women about the use of tamoxifen, as a chemopreventive agent. The tables of Claus and colleagues¹³⁸ also determine breast cancer risk, taking into consideration the number and age of first- and second-degree female relatives with breast cancer. Despite this, the tables of Claus and colleagues¹³⁸ will also underestimate the risk of a woman developing breast cancer if she has a hereditary predisposition to developing breast cancer. Again, when used in the provision of cancer risk assessment and counseling, the tables of Claus and colleagues¹³⁸ are a helpful tool to provide a breast cancer risk estimate for a woman whose family history is not highly suggestive of a known hereditary cancer syndrome.

A second group of models (BRCAPRO, Myriad II, Penn II, BOADICEA, TIRER-CUZICK, Couch, and Shattuck-Eidens) are designed to estimate the likelihood of identifying a mutation in the *BRCA1* or *BRCA2* genes.^{5,139–142} These models have strengths and limitations that health care providers need to be familiar with to use and interpret them appropriately.^{143–145} For example, the Couch and colleagues¹⁴⁰ and Shattuck-Eidens and colleagues¹⁴¹ models use summarization of family history to estimate the likelihood that an individual carries a mutation in the *BRCA1* gene, and do not estimate the chance of a *BRCA2* mutation. The BRCAPRO model evaluates the probability that an individual is a carrier of a *BRCA* mutation using family history and Bayes' theorem.¹³⁹ However, BRCAPRO only incorporates relevant family history up to the second degree relatives, thereby, potentially underestimating the probability of *BRCA* mutations in individuals with an extended family history. The BRCAPRO model also does not incorporate pancreatic or prostate cancer risk into its risk estimate, thereby, leading to an underestimate of risk. There are currently no statistical models that predict the likelihood of identifying mutations in the *PTEN* or *TP53* genes.

When using these risk models it is important for to remember that risk calculations may vary because of the

different factors assessed, and clients should be educated about the limitations of these risk calculations so that they can put their risk estimates into context. Therefore, the health care provider should use clinical judgment so clients receive the most precise risk assessment.

Assessing psychosocial issues is integral to how we relay risk information. By identifying and analyzing the psychosocial issues during the cancer genetic counseling process, the health care provider can appreciate the different aspects of an individual's background, which affects their risk perception.^{146,147} Identifying the psychosocial issues may also help the health care provider and the client understand how an individual's emotions and psychosocial factors impact the utilization of the information presented during a genetic counseling session.^{146,148,149} In addition, recognizing the psychosocial factors at play allow a health care professional to provide anticipatory guidance.

Genetic Testing

Molecular analysis of the *BRCA1*, *BRCA2*, *PTEN*, and *TP53* genes is commercially available, and it is well established which patients should be offered genetic testing for the conditions associated with mutations in these genes. According to the American Society of Clinical Oncology,¹⁵⁰ individuals should be offered testing when they have a personal or family history suspicious for a cancer predisposition syndrome, the test results can be adequately interpreted, and the results will assist in the diagnosis or influence medical management of the individual or their at-risk family members. Pre- and posttest education and informed consent should be part of the genetic testing process for hereditary cancer susceptibility conditions.^{130,150,151} The process of genetic counseling allows individuals ample opportunity to educate themselves about the benefits, limitations, and risks of genetic testing, as well as the possible benefits and risks of cancer early detection and prevention strategies, to make an informed decision. In addition, although initially it is one individual being tested, individuals are encouraged through genetic counseling to consider how results from testing might affect not only them personally, but their family members as well. Individuals can also begin to plan how they will use results to influence their medical management and health behaviors.

Ideally, genetic testing should be performed on an individual who has been diagnosed with cancer because it provides the most information for the entire family. There are four possible test outcomes: positive (deleterious), true-negative, uninformative, and a variant of uncertain significance (Table 3). True-positive results are deleterious mutations that prevent normal gene function. A positive result confirms the diagnosis of a hereditary cancer syndrome and confers an increased risk for the cancers associated with the condition. At-risk family members can undergo genetic analysis for the specific mutation identified in the family to determine their risk status, and such testing will be highly sensitive.

Table 3. Genetic Test Results

Result	Interpretation
True positive (deleterious)	Mutation identified is associated with increased cancer risk
True negative	No mutation was identified in an individual who has a known deleterious mutation in the family. Therefore, this individual is not at an increased risk for developing cancer
Uninformative	No mutation has been identified and a deleterious mutation has not been previously identified in the family. The individual and family members may still be at increased risk for cancer and medical recommendations should be based on family history
Variant of uncertain significance	Mutation identified but its clinical significance is not known. The individual and family members may still be at increased risk for cancer and medical recommendations should be based on family history

A true-negative result can occur only when there is a known deleterious mutation in the family. For example, an individual is found not to have the *BRCA1* mutation previously identified in her father. Individuals with true-negative results are not at an increased risk for developing the cancers associated with the hereditary cancer syndrome. Instead, their risk for developing cancer is believed to be the same as that in the general population. There is data from a few studies, both prospective and retrospective, suggesting that individuals who test negative for known familial mutations in cancer susceptibility genes could still be at increased risk for cancers, attributed to shared genetic modifiers, when compared to the general population.^{152–154} However, it is important to note that the significant findings of increased risk were derived from retrospective data that may be subject to ascertainment bias and prospective data that did not reach statistical significance because of small sample sizes. Thus, more data are necessary to confirm these findings, as, if true, it could impact the management for these individuals.

Because some affected family members may be deceased or unwilling to undergo testing, it is not always feasible to test an affected family member. In other situations, an individual may choose to undergo genetic testing without knowing their family history, as in cases of adoption, or because of high cancer anxiety. In this scenario, a negative genetic test result does not exclude the possibility of a hereditary cancer predisposition. First, given limitations in current testing technology, a negative result does not exclude the possibility that there is an undetectable mutation in the gene being analyzed.⁵³ Second, a negative result in this situation also does not exclude the possibility that the person may carry a mutation in a different cancer susceptibility gene that has not yet been tested. Counseling of individuals in this situation must stress that they still have a residual risk for developing cancer so that individuals do not have a false

sense of reassurance. Third, it is possible that the unaffected family member does not carry a potentially identifiable deleterious mutation that is placing other family members at risk.

Variants of uncertain significance (VUS) are typically missense mutations that are of unknown functional significance and intronic mutations not known to be involved in mRNA processing.^{130,155} Thus, the risk consequences of VUS are often unknown. With *BRCA1* and *BRCA2* alone, it is estimated that VUS are identified in 10 to 13% of individuals who undergo full sequence analysis.^{20,155} The incidence of VUS in *TP53* and *PTEN* is not well defined. VUS can occur in individuals who are affected with cancer, as well as those who are unaffected. In addition, the likelihood of identifying a VUS varies by ethnicity. Testing may be performed to determine whether the VUS tracks with the cancer in the family; however, without a functional assay to determine the implication of the gene change, the significance of the mutation remains unknown.^{5,53} In cases in which a VUS is identified, predictive testing for at-risk family members cannot be performed. Additionally, medical management must be based on the known family history rather than the presence or absence of the VUS.

Benefits, Risks, and Limitations of Genetic Testing

Individuals undergoing cancer genetic counseling must understand the benefits, limitations, and risks of genetic testing to make an informed decision about whether to use testing. The potential impact on medical management is an obvious benefit. A woman who tests positive for a known familial gene mutation can make informed decisions about when she should start cancer surveillance, the type of cancer surveillance necessary, and whether she should consider prophylactic surgeries. A woman with a true negative result can avoid unnecessary screening and/or surgeries. Genetic testing can clarify risk status, not only for the person being tested, but for other family members. If a deleterious mutation is identified, it allows for targeted mutation testing in at-risk family members. Genetic test results may also allay emotional and psychological fears associated with the uncertainty surrounding their risk status before undergoing genetic testing.¹⁵⁶

Individuals should also be apprised of the limitations to genetic testing. As discussed previously, a negative result in an individual without cancer and without a known mutation in the family does not rule out a hereditary cancer syndrome in the family or the individual being tested. A family history of cancer could also be attributable to a gene that was not tested or a gene in which testing is not yet available. Inaccurate family history may also lead to inappropriate genetic testing which limits the accuracy of the result interpretation and risk assessment. In addition, individuals undergoing genetic testing may not have a detectable mutation based on current technological limitations.

Although the majority of the literature assessing the psychological impact of cancer genetic testing has not

demonstrated any significant long-term negative consequences, several research studies have documented that individuals who undergo cancer susceptibility testing experience a range of emotions, including anxiety, distress, and depression.^{147,149,157-160} Guilt is another powerful emotional response individuals may experience, arising from the fear of passing the mutation on to one's children.¹⁶¹ In addition, some individuals experience guilt for not inheriting a mutation that has been identified in another family member.^{147,149,158,162} Family systems may be disrupted because some individuals will want the information genetic counseling and testing can offer and others will not. In some families, affected individuals may feel coerced into undergoing genetic testing to aid in determining the risk status of other family members.¹³¹ This disruption may occur not only between parents, children, and siblings, but also between spouses and partners.¹⁴⁷

Genetic testing also has economic risks associated with it because the cost for testing can range from a few hundred dollars to more than \$3000 depending on the genes being tested and the type of testing being performed (targeted mutation analysis versus full sequencing). Although the majority of health insurance companies are covering the costs of genetic testing, some may not reimburse for counseling or testing services. Some insurance companies may only cover a portion of the cost. Individuals considering testing may want to consider determining their level of insurance coverage before proceeding with testing.¹³⁰ In addition, when insurance coverage is broached, it may be necessary to address concerns regarding potential insurance discrimination. Although, to date, there is no published documentation of insurance discrimination for hereditary cancer syndrome testing, some individuals are still concerned.¹⁶³ Fear of insurance discrimination can be so powerful that individuals may not pursue genetic testing or delay the testing.¹⁶⁴ Pretest genetic counseling should, therefore, include a discussion about the lack of documented discrimination cases. Counseling should also include a review about the current federal legislation providing protection against genetic discrimination in health insurance, such as the Federal Health Insurance Portability and Accountability Act of 1996, which prevents group health plans from using genetic information as a pre-existing condition to limit or deny coverage,^{130,165} and the state laws regarding health insurance discrimination, keeping in mind that these laws vary from state to state.¹³⁰

Summary

Only 5 to 10% of breast cancer cases are attributable to highly penetrant Mendelian cancer susceptibility genes. Currently, hereditary breast and ovarian cancer syndrome, LFS, and Cowden syndrome are the most common conditions being tested for in the clinical setting for individuals with personal or family histories of breast cancer. Identification of those individuals who would benefit from genetic testing still relies primarily on interpretation of a thorough family history, although pathological features of cancers may assist in risk assessment. Genetic

counseling for these hereditary breast cancer syndromes is the standard of care and includes the process of obtaining informed consent through a thorough discussion of the risks, benefits, and limitations of risk assessment, genetic testing, result interpretation, and medical management options. Ultimately, genetic testing can assist in the identification of at-risk individuals who could benefit from improved medical management.

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