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Committee on Genetics
This Committee Opinion was developed by the American College of Obstetricians and Gynecologists’ (ACOG) Committee on Genetics in collaboration with the Society of Gynecologic Oncology liaison members, Lee-may Chen, MD and Susan Modesitt, MD.

Hereditary Cancer Syndromes and Risk Assessment

ABSTRACT: A hereditary cancer syndrome is a genetic predisposition to certain types of cancer, often with onset at an early age, caused by inherited pathogenic variants in one or more genes. Most hereditary cancer syndromes exhibit autosomal dominant inheritance. The most common hereditary cancer syndromes related to women’s cancer include hereditary breast and ovarian cancer syndrome, Lynch syndrome, Li–Fraumeni syndrome, Cowden syndrome, Peutz–Jeghers syndrome, and hereditary diffuse gastric cancer. A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. Assessments should be performed by obstetrician-gynecologists or other obstetric–gynecologic care providers and should be updated regularly. An assessment includes information on personal and family history, including pathology, imaging reports, and evaluation of other medical risk factors for cancer. If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both. Currently, genetic testing is guided by personal history, family history, pedigree analysis and, in some cases, risk models that may include pathology reports and confirmation of cancer diagnoses with medical records, death certificates, or both. Counseling before and after genetic testing is an important part of the process to discuss rationale for any genetic testing, disclose results, define other cancer risks, identify educational needs, and secure referrals if necessary for ongoing management. This revision includes updates related to hereditary breast and ovarian cancer, cascade testing, and referrals to genetics specialists.

Recommendations

- A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. Assessments should be performed by obstetrician-gynecologists or other obstetric–gynecologic care providers and should be updated regularly.
- If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both.
- Genetic testing may be performed using a panel of multiple genes through next-generation sequencing technology. This multigene testing process increases the likelihood of finding variants of unknown significance, and it also allows for testing for pathogenic and likely pathogenic variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype (or multiple phenotypes).

Introduction

A hereditary cancer syndrome is a genetic predisposition to certain types of cancer, often with onset at an early age, caused by inherited pathogenic variants in one or more genes. Although a mutation (or variant) is defined as any change in the DNA sequence away from normal,
a pathogenic variant, or deleterious mutation, is a genetic alteration that increases an individual’s predisposition to a certain disease or disorder. Frequently, these predisposing pathogenic variants also result in cancer that affects multiple organs within the same individual or within a family. Most hereditary cancer syndromes exhibit autosomal dominant inheritance. Cases of cancer commonly encountered by obstetrician–gynecologists or other obstetric–gynecologic care providers, such as breast cancer, ovarian cancer, endometrial and colon cancer, may be part of a specific hereditary cancer syndrome. The most common hereditary cancer syndromes related to women’s cancer include hereditary breast and ovarian cancer syndrome, Lynch syndrome, Li–Fraumeni syndrome, Cowden syndrome, Peutz–Jeghers syndrome, and hereditary diffuse gastric cancer (Table 1).

Obstetrician–gynecologists or other obstetric–gynecologic care providers play an important role in the identification and referral of women at risk of these conditions. All women with a personal history of epithelial ovarian cancer or a first degree relative with epithelial ovarian cancer should be immediately referred for genetic counseling and testing, and all women with endometrial or colon cancer should be evaluated for hereditary cancer risk (1, 2). The focus of this Committee Opinion is hereditary cancer syndromes that include increased risks of breast cancer, ovarian cancer, and endometrial cancer. This revision includes updates related to hereditary breast and ovarian cancer, cascade testing, and referrals to genetics specialists.

Family and Medical History Screening
A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. This assessment should be performed by obstetrician–gynecologists or other obstetric–gynecologic care providers and should be updated regularly. An assessment includes information on personal and family history, including pathology, imaging reports, and evaluation of other medical risk factors for cancer.

A patient intake form, which includes a review of systems and conditions that may exist in the patient or her family, is used in many office settings to gather information quickly. The American College of Obstetricians and Gynecologists’ Committee Opinion No. 478, *Family History as a Risk Assessment Tool*, establishes the general concept of collecting a family history and constructing a pedigree. Online versions of an intake form are available for patients and health care providers. For example, the Surgeon General’s “My Family Health Portrait,” is a web-based program in which patients may create a comprehensive family history that can be shared with family and health care providers (3).

Commercial genetic testing is now available through several direct-to-consumer venues for a variety of purposes. The most popular tests are marketed to offer clues about a person’s ancestry or to use genetic variations to make predictions about an individual’s health. Customers can send the company a DNA sample and receive their results without involving any health care provider or health insurance company. However, the results of genetic tests may be challenging to interpret without expert guidance. A positive result does not equate with a clinical diagnosis, and a negative result is not indicative of the absence of disease risk (in particular, the ancestry companies test for only a few deleterious variants of a few genes). The context of type of test

**Table 1. Summary of Syndromes With Malignant Manifestations Associated With Breast and Ovarian Cancer**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Breast Cancer</th>
<th>Ovarian Cancer</th>
<th>Endometrial Cancer</th>
<th>Colon Cancer</th>
<th>Other Types of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Pancreatic, prostate, and melanoma</td>
</tr>
<tr>
<td>Lynch</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Gastric, ureteral, biliary, pancreatic, glioblastoma, renal pelvis</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>Sarcomas, brain, adrenocortical</td>
</tr>
<tr>
<td>Cowden</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Benign mucocutaneous lesions, thyroid, gastrointestinal hamartomas</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Cervical adenoma malignum, gastrointestinal hamartomas, pancreatic, gastric, small bowel</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>Gastric, colorectal</td>
</tr>
</tbody>
</table>

performed, and other health factors including family history must be considered.

Additionally, both commercial and research genetic testing of malignant tumor tissue (also known as somatic tumor testing) is being used more often in oncology practices to identify potential targeted therapies for cancer treatment. These tests also require expertise and context for clinical application. It should be clear that although tumor sequencing reflects genetic testing of somatic cells, hereditary cancer syndromes are attributable to germline testing results.

The American Society of Clinical Oncology Cancer Genetics Subcommittee convened a consensus conference in February 2012, which led to the American Society of Clinical Oncology Expert Statement: Collection and Use of a Cancer Family History for Oncology Providers (4). Similar to the recommendations in the American Society of Clinical Oncology Expert Statement, the hereditary cancer risk assessment should be updated regularly to reflect changes in the patient’s medical and family history. Screening should include, at a minimum, a personal cancer history and a first-degree and second-degree relative cancer history that includes a description of the type of primary cancer, the age of cancer onset, and the lineage (paternal versus maternal) of the family member (Box 1). In addition, a patient’s ethnic background can influence her genetic risk, and this information is relevant in assessing a patient’s predisposition to a hereditary cancer syndrome (eg, BRCA mutations and Ashkenazi Jewish descent).

Certain features of a person’s personal or family medical history suggest a possible hereditary cancer syndrome. Additional clues that a hereditary cancer syndrome may be present include the following (4):

- Cancer diagnosed at an unusually young age or less than 50 years for breast, ovarian, or colon cancer
- Several different types of cancer in the same person
- Multiple primary tumors, especially in the same organ (such as the breast or colon), in a single individual
- Several close blood relatives that have the same type of cancer (eg, a mother, daughter, and sisters with breast cancer), especially when blood relatives are on the same side of the family
- Unusual presentation of a specific type of cancer (eg, breast cancer in a man)
- The presence of specific benign conditions, specifically skin growths or skeletal abnormalities, that are known to be associated with inherited cancer syndromes
- Occurrence of certain types of adult cancer in which the probability of harboring a hereditary cancer syndrome is high:
  - Triple-negative breast cancer (lack of expression of estrogen and progesterone receptors and lack of ERBB2 (also known as HER2 or HER2/neu) over-expression, suggesting hereditary breast and ovarian cancer syndrome [30% when less than age 60 years]) (5)
  - Epithelial ovarian cancer, fallopian tube cancer, or peritoneal cancer, especially serious histology (suggesting hereditary breast and ovarian cancer syndrome [10–15%]) (6)
  - Colorectal cancer with DNA mismatch repair deficiency (suggesting Lynch syndrome [24%]) (7)
  - Endometrial cancer with DNA mismatch repair deficiency (suggesting Lynch syndrome [12%]) (8)

**Box 1. Recommended Key Elements for Minimum Adequate Cancer Family History**

Family history should be taken at diagnosis and updated periodically.

Key components should include information about the following:

- First-degree relatives: siblings, parents, children
- Second-degree relatives: grandparents, aunts, uncles, grandchildren, nieces, nephews, half-siblings
- Maternal and paternal sides
- Ashkenazi ancestry
- For each cancer case in the family, establish
  - Age at cancer diagnosis
  - Type of primary cancer


**Referral to a Genetics Specialist**

There are numerous resources that address genetic counseling as a means of identifying patients at risk of a specific inherited cancer or hereditary cancer syndrome (9, 10). If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both.

Genetic testing may be performed using a panel of multiple genes through next-generation sequencing technology. This multigene testing process increases the likelihood of finding variants of unknown significance, but it also allows for testing for pathogenic and likely pathogenic variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype (or multiple phenotypes), because there often is more than one syndrome that can be the root cause of cancer for a family.
Although such condition-specific resources are valuable, complex algorithms and narrow focus limit their usefulness in a clinical setting. The 2015 practice guideline published by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors includes a list of cancer types and benign conditions that can be cross-referenced to cancer-family syndromes so the appropriateness of cancer genetic counseling can be determined but clinicians should have a low threshold for referring any woman with a suggesting personal or family cancer history for evaluation (11).

Genetic counseling is the process of evaluating risk, identifying appropriate patients for genetic testing, reviewing the limitations, determining risks, benefits and scope of testing, and obtaining informed consent after patient education. Although some high-risk populations, such as Ashkenazi Jews, may consider population genetic testing given the high frequency of pathogenic variants in BRCA1 and BRCA2, there is less emphasis on population testing overall, but rather identification of at-risk individuals for referral. Currently, genetic testing is guided by personal history, family history, pedigree analysis and, in some cases, risk models that may include pathology reports and confirmation of diagnoses with medical records, death certificates, or both. Counseling after genetic testing is an important part of the process to discuss rationale for any genetic testing, disclose results, define other cancer risks, identify educational needs, and secure referrals if necessary for ongoing management. In addition, counseling after genetic testing should include discussion of cancer risk for other family members as well as clear recommendations for whom cascade testing is indicated when a pathogenic variant is diagnosed (12). Referral Indications for Cancer Predisposition Assessment, a practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors, can help identify patients who would benefit from genetic counseling (11).

**Most Common Hereditary Cancer Syndromes Related to Gynecologic Cancer**

**Hereditary Breast and Ovarian Cancer Syndrome**

Hereditary breast and ovarian cancer syndrome is caused most commonly by germline pathogenic variants in one of the autosomal dominant DNA repair genes BRCA1 and BRCA2. However, genes such as ATM, BRIPI, CDH1, CHEK2, NBN, NF1, PALB2, RAD51C, RAD51D and others are also implicated in a significant number of hereditary breast and ovarian cancer syndromes (1, 13). Some of these genes (CDH1, CHEK2) are considered actionable for their increased breast cancer risk, but there is insufficient evidence for a clear increased risk for ovarian cancer. Other genes (BRIP1, RAD51C, RAD51D) are associated with an increased ovarian cancer risk without increased breast cancer risk. Although most cases of breast cancer and ovarian cancer in the United States occur sporadically, pathogenic BRCA1 and BRCA2 mutations are present in 5–15% of cases of these types of cancer (14). Pathogenic variants in BRCA2 also can be associated with pancreatic cancer and melanoma. In men, pathogenic variants in BRCA2 are associated with breast cancer and prostate cancer. Therefore, it is important to ask male and female relatives about maternal and paternal ancestry. Hereditary breast and ovarian cancer syndrome, as well as many of the other hereditary cancer syndromes, displays incomplete penetrance (ie, not everyone with a gene mutation will develop cancer). Women with hereditary breast and ovarian cancer syndrome have a 65–74% lifetime risk of breast cancer and a 39–46% (BRCA1) or a 12–20% (BRCA2) risk of ovarian cancer (15, 16) and are recommended for screening or risk-reducing surgery, or both, to improve cancer morbidity and mortality and overall mortality (17). The carrier frequency of hereditary breast and ovarian cancer syndrome is approximately 1 in 500 individuals in the general population, but it has a prevalence of 1 in 40 individuals in the Ashkenazi Jewish population (18).

**Lynch Syndrome**

Approximately 3–5% of cases of uterine cancer are attributable to a hereditary cause, and most of these cases are due to Lynch syndrome, also known as “hereditary non-polyposis colorectal cancer (HNPCC),” a highly penetrant autosomal dominant hereditary cancer syndrome caused by defects in the DNA mismatch repair genes, including MLH1, MSH2, MSH6, PMS2, and EPCAM. Lynch syndrome accounts for most cases of hereditary uterine cancer and colorectal cancer and is the second most common cause of inherited ovarian cancer (after hereditary breast and ovarian cancer syndrome). The presence of Lynch syndrome increases the lifetime risk of colon cancer (52–82%), endometrial cancer (25–60%), and ovarian cancer (4–24%) (11, 19). It has a population prevalence of approximately 1 in 600 to 1 in 3,000 individuals (2).

Other neoplasms associated with Lynch syndrome include gastric cancer, small-bowel cancer, hepatobiliary cancer, and renal pelvis and ureteral cancer, and potentially some types of breast cancer, certain brain tumors, and sebaceous skin tumors (2). By identifying individuals at risk of Lynch syndrome, health care providers are able to offer screening and prevention strategies to reduce morbidity and mortality due to this syndrome. For more information on identifying individuals at risk of Lynch syndrome, see American College of Obstetricians and Gynecologists Practice Bulletin No. 147, Lynch Syndrome, as well as the 2015 practice guideline published by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors (2, 11).

**Li–Fraumeni Syndrome**

Li–Fraumeni syndrome is a rare autosomal dominant condition with increased risk of multiple tumors,
including osteosarcoma, breast cancer, colon cancer, adrenocortical carcinoma, leukemia and lymphoma, and brain cancer. The exact prevalence of Li–Fraumeni syndrome is unknown. One U.S. registry of patients with Li–Fraumeni syndrome suggests that approximately 400 individuals from 64 families may have this condition (20). Li–Fraumeni syndrome is caused by germline mutations in the tumor suppressor gene TP53. In fact, more than 70% of individuals with a clinical diagnosis of Li–Fraumeni syndrome have a detectable mutation in the TP53 gene (21). Li–Fraumeni syndrome is highly penetrant, with a 90% risk of cancer by age 60 years (22). Patients with a diagnosis of Li–Fraumeni syndrome-associated malignancies (eg, soft tissue sarcomas, osteosarcomas, premenopausal breast cancer, brain tumors, and adrenocortical carcinomas), especially with multiple family members with these types of cancer (due to the high penetrance of the disease), should be referred to specialists in cancer genetics for further evaluation for Li–Fraumeni syndrome.

Cowden Syndrome
Cowden syndrome is an autosomal dominant condition caused by pathogenic variants in the phosphatase and tensin (PTEN) gene, which is involved in cell cycle control (23). It is relatively rare, with a population prevalence of 1 in 200,000 (24, 25). Cowden syndrome is one of the hamartomatous syndromes and is characterized by benign and malignant neoplasms of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly (26, 27). Pathognomonic skin lesions, including papillomatous papules on the face and mucous membranes (Fig. 1), are nearly always present by age 30 years. Cowden syndrome carries a high lifetime risk of breast cancer (25–50%), endometrial cancer (5–10%), and colon cancer (9%), and thyroid cancer and should be suspected in any family with Cowden syndrome-associated neoplasms and conditions, which are classified as pathognomonic, major and minor criteria (11).

Peutz-Jeghers Syndrome
Peutz–Jeghers syndrome is an autosomal dominant condition caused by pathogenic variants in the serine/threonine kinase 11 (STK11) gene. It is characterized by the presence of two of the following three criteria: 1) two or more hamartomatous polyps throughout the gastrointestinal tract; 2) mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers (Fig. 2); and 3) a family history of Peutz–Jeghers syndrome (11). Peutz–Jeghers syndrome also is associated with an increased risk of breast cancer (50% lifetime risk), ovarian sex cord stromal cancer, cervical cancer (especially the histologic diagnosis of adenoma malignum), uterine cancer, pancreatic cancer, lung cancer, gastric cancer, and colon cancer.

Hereditary Diffuse Gastric Cancer
Hereditary diffuse gastric cancer is characterized by an increased risk of diffuse gastric cancer, lobular breast cancer, and colorectal cancer, and is attributable to pathogenic variants of the CDH1 gene. The lifetime risk for women with germline mutations in CDH1 is reported to be 42% (28).

Conclusion
Obstetrician–gynecologists can evaluate for familial cancer syndromes and refer appropriate patients for genetic counseling and testing and potential life-saving
cancer risk reduction measures. The use of multigene panel testing and cascade testing may identify asymptomatic at-risk individuals who should then be referred to appropriate specialists or centers for regular follow-up, surveillance, and prophylactic surgery when indicated.

**For More Information**

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/More-Info/Cancer-Genetics.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists’ endorsement of the organization, the organization’s website, or the content of the resource. The resources may change without notice.

**References**


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