Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions

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Introduction

The hallmarks of hereditary cancer syndromes include multiple affected family members, early age of onset, and the presence of multiple and/or bilateral primary cancers [1–4]. Although such clinical markers have long been recognized, it is now possible to identify some of the genetic alterations that predispose individuals to inherited breast, gynecologic and gastrointestinal cancers [5–11]. A recent study found that 24% of unselected ovarian cancers had a germline mutation, including 18% with a BRCA1 or BRCA2 mutation [12].

Women with mutations in the BRCA1 or BRCA2 associated with Hereditary Breast & Ovarian Cancer syndrome, have up to an 85% lifetime risk of breast cancer and up to a 46% lifetime risk of ovarian, tubal, and peritoneal cancers. Similarly, women with mutations in the DNA mismatch repair genes, MLH1, MSH2, MSH6, or PMS2, associated with the Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome, have up to a 40–60% lifetime risk of both endometrial and colorectal cancers as well as a 9–12% lifetime risk of ovarian cancer. Mutations in other genes including TP53, PTEN, and STK11 are responsible for hereditary syndromes associated with gynecologic, breast, and other cancers. Evaluation of the likelihood of a patient having one of these gynecologic cancer predisposition syndromes enables physicians to provide individualized assessments of cancer risk, as well as the opportunity to provide tailored screening and prevention strategies such as surveillance, chemoprevention, and prophylactic surgery that may reduce the morbidity and mortality associated with these syndromes. Evaluation for the presence of a hereditary cancer syndrome is a process that includes assessment of clinical and tumor characteristics, education and counseling conducted by a provider with expertise in cancer genetics, and may include genetic testing after appropriate consent is obtained. This commentary provides guidance on identification of patients who may benefit from assessment for the presence of a hereditary breast and/or gynecologic cancer syndrome.

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Abstract

Women with germline mutations in the cancer susceptibility genes, BRCA1 or BRCA2, associated with Hereditary Breast & Ovarian Cancer syndrome, have up to an 85% lifetime risk of breast cancer and up to a 46% lifetime risk of ovarian, tubal, and peritoneal cancers. Similarly, women with mutations in the DNA mismatch repair genes, MLH1, MSH2, MSH6, or PMS2, associated with the Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome, have up to a 40–60% lifetime risk of both endometrial and colorectal cancers as well as a 9–12% lifetime risk of ovarian cancer. Mutations in other genes including TP53, PTEN, and STK11 are responsible for hereditary syndromes associated with gynecologic, breast, and other cancers. Evaluation of the likelihood of a patient having one of these gynecologic cancer predisposition syndromes enables physicians to provide individualized assessments of cancer risk, as well as the opportunity to provide tailored screening and prevention strategies such as surveillance, chemoprevention, and prophylactic surgery that may reduce the morbidity and mortality associated with these syndromes. Evaluation for the presence of a hereditary cancer syndrome is a process that includes assessment of clinical and tumor characteristics, education and counseling conducted by a provider with expertise in cancer genetics, and may include genetic testing after appropriate consent is obtained. This commentary provides guidance on identification of patients who may benefit from assessment for the presence of a hereditary breast and/or gynecologic cancer syndrome.

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Introduction

The hallmarks of hereditary cancer syndromes include multiple affected family members, early age of onset, and the presence of multiple and/or bilateral primary cancers [1–4]. Although such clinical markers have long been recognized, it is now possible to identify some of the genetic alterations that predispose individuals to inherited...
Germline mutations in the PTEN gene, which underlies Cowden syndrome, have been associated with a 19–28% risk of endometrial cancer by age 70, however, in light of lack of censoring of endometrial cancer incidence rates for previous hysterectomy in these studies, the true risk may be higher in women with an intact uterus. In addition to endometrial cancer risk, women with germline mutations in the PTEN gene have up to a 50% risk of breast cancer and 3–10% risk of thyroid cancer [28–31]. Women who carry germline mutations in the TP53 gene, associated with Li Fraumeni syndrome, have up to a 60% lifetime risk of breast cancer, in addition to other “core” cancers that include sarcomas, brain, and adrenocortical carcinomas [32]. The less common Peutz–Jeghers syndrome, caused by mutations in STK11/LKB1 gene, is associated with elevated risk of cervical (adenoma malignum), ovarian (sex cord stromal tumors) and breast cancers (10%, 21%, and 50% lifetime risk, respectively) [33].

Although HBOC and Lynch are the most well-known syndromes associated with ovarian cancer, recently at least three new genes, including BRIP1, RAD51D, and RAD51C, have been described to be associated with a lifetime risk of 10–15% [12,34–36]. PALB2 mutations have been identified in breast and ovarian cancer families and unselected ovarian cancer cases though a clear increased relative risk has not been established [37,38]. Most recently, germline mutations in the DICER1 and SMARC4 genes have been identified to be associated with Sertoli–Leydig tumors and ovarian small cell carcinoma, respectively [39–44]. It is expected that the list of genes associated with ovarian cancer will continue to increase in the very near future.

Evaluation for the presence of a hereditary cancer syndrome enables physicians to provide individualized and quantified assessment of cancer risk, as well as options for tailored screening and prevention strategies that may reduce morbidity associated with the development of malignancy. Strategies that have been demonstrated to improve outcomes in individuals at inherited risk include breast screening with magnetic resonance imaging (MRI) [45,46], colorectal cancer screening with colonoscopy [47], risk-reducing surgery, and chemoprevention (oral contraceptives for Ov/FT/PC risk). Though some studies suggest that tamoxifen, a selective estrogen receptor modulator, may reduce the risk of contralateral breast cancer in affected BRCA1/2 mutation carriers [48,49], the limited sample size of the NSABP-P1 study, prohibits definitive conclusions from being drawn on its benefit to unaffected individuals.

It is estimated that in 2012 only 24% of newly diagnosed women with ovarian carcinoma in the United States received genetic testing for BRCA1 and BRCA2 mutations, despite current NCCN guidelines recommending genetic counseling and testing be offered to all women with this disease [50]. It is clear that only a small minority of women with an inherited predisposition to breast and Ov/FT/PC have been identified. Research has shown that women with an inherited mutation who have fallopian tubes and ovaries removed reduce their risk of ovarian cancer by over 90%, and also reduce their cancer-related and overall mortality [51]. In addition, BRCA1 and BRCA2-related Ov/FT/PC are associated with improved survival, responsiveness to platinum chemotherapy and novel therapies such as PARP inhibitors [52]. Knowledge of genetic status will make a difference in the lives of patients and their families, both by prevention and therapy of associated cancers. Because of the direct impact on the care of the patient as well as the value of preventing cancer in family members, all women with epithelial ovarian cancer should receive genetic counseling and be offered genetic testing regardless of age or family history.

The Society of Gynecologic Oncology (SGO) is committed to encouraging the medical community to identify women who may benefit from assessment for the presence of a hereditary cancer syndrome.

Changing landscape of genetic testing

The June 2013 Supreme Court ruling was that “a naturally occurring DNA segment” (i.e., a gene) cannot be patented. This was a unanimous decision by the Court. Prior to this decision, Myriad Genetics held the patent on the BRCA1 and BRCA2 genes and therefore the vast majority of testing in the US was performed by their commercial testing facility at a cost of approximately $3000 and up to $4000 for the most comprehensive panel. The Court decided that specific proprietary methodology in genetic testing and also synthetically-generated strands of DNA, (called cDNA), are eligible for patent protection. Currently BRCA1 and BRCA2 testing can be obtained individually or as part of multiplex gene panels from a variety of commercial laboratories. Panels and testing technology vary with each laboratory but the expectation is that in the future, more panels of genes linked to risk will be available at a lower cost.

Several for-profit commercial entities now offer direct-to-consumer marketing of cancer risk panel tests, including the use of single nucleotide polymorphism (SNP) based tests. Cost for such a SNP-based analysis of saliva can run as low as $99. When measured at a population-level, risk-associated SNPs occur more commonly in those individuals with a condition than without; as such, they are considered to be associated with cancer but are not necessarily causative, and do not result in levels of risk that would currently alter clinical recommendations. Recently, the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) reported two new genetic risk modifiers (BRCA1-specific SNP rs4691139 and SNP rs17631303, located at 4q32.3 and 17q21.31, respectively), which increased the risk of ovarian cancer in both BRCA1 and BRCA2 mutation carriers [53]. Such findings may pave the way for further individualization of ovarian cancer risk assessment in BRCA1/2 mutation carriers.

Our understanding of genetic predisposition for particular cancers is rapidly changing from individual genes and syndromes to multiplex testing for a number of cancer susceptibility genes to assess cancer risk. Such multiplex panels can be chosen based upon particular cancer patterns in families as well as suggested by ethnicity with certain inherited mutations more common in certain ethnic groups, e.g., Ashkenazi Jewish, French Canadians, Hispanic families. With the increase in complexity of testing technology, the uncertainty in the interpretation of the results and the range of potentially identifiable cancer-risk, the need for evaluating the likelihood of the presence of a hereditary cancer syndrome, choosing the appropriate test or panel, and interpreting the result, all clearly argue that the first step in patient assessment should be genetic counseling.

It is important to emphasize that assessment for the presence of an inherited cancer predisposition syndrome is a process that:

- Includes assessment of likelihood of the presence of a genetic predisposition to cancer, education and counseling;
- May include evaluation of available tumor, with testing including immunohistochemistry and microsatellite instability;
- Is conducted by a physician, genetic counselor or other providers with expertise in cancer genetics;
- May include germline genetic testing if desired after appropriate counseling and consent have been obtained.

This commentary provides guidance to physicians and other health professionals in the identification of patients who may benefit from assessment for the presence of an inherited predisposition for breast, ovarian and endometrial cancers.

These guidelines were developed through a series of face-to-face meetings and conference calls of the SGO Education Resource Panel for Hereditary Cancers, and updated through the SGO Clinical Practice Committee. The guidelines reflect the synthesis of a detailed literature review conducted by the panel’s members as well as comments from gynecologic oncologists, general gynecologists, genetic counselors, medical oncologists and other gynecologic cancer professionals. The final recommendations were reviewed by the Clinical Practice Committee and the Publications Committee of the SGO, both of which provided valuable feedback prior to publication.

Recommendations

Given the potential impact on clinical care for both patients as well as their close family members, the SGO recommends that individuals...
with a likelihood of inherited predisposition to cancer based on personal or family history should be offered genetic counseling. Referral for counseling and consideration of genetic testing for HBOC genes should be offered to women who meet the criteria outlined in Table 1. While the specific criteria outlined in Tables 1-2 identify individuals that generally meet these thresholds for gynecologic malignancy, there are some patients who do not meet one of the specific criteria listed who may still benefit from assessment for an inherited cancer predisposition. Situations which may warrant a lower threshold for genetic risk assessment include:

- Families with few female relatives as this may lead to an under-representation of female cancers despite the presence of a predisposing family mutation [55,56];
- Hysterectomy and/or oophorectomy at a young age in multiple family members as this might mask a hereditary gynecologic cancer predisposition [57];
- Presence of adoption in the lineage.

In light of the increasing complexity of available genetic tests, and because the significance of positive results is not always clear and negative results may be falsely reassuring, it is recommended that patients begin with genetic counseling to determine appropriate testing options. Following testing, it is also important to have experts available to interpret results and recommend treatment planning, ideally as part of a multidisciplinary team of providers [54]. It is also recognized that specialized genetic counseling services and/or access to individuals with expertise in cancer genetics may not be readily available in all geographic locations. In such circumstances, prior to undergoing genetic testing, it remains preferable for patients to receive counseling, which may be provided by individuals who are not board certified genetic counselors, but who have received appropriate training in cancer genetic counseling (e.g., advanced-practice professionals, R.N.s). Alternatively, as technology has evolved, several telemedicine services have developed that deliver genetic counseling services via telephone. In a recent study that compared telephone delivery of BRCA1/2 genetic counseling to in-person delivery, telephone counseling was found to be non-inferior to in-person counseling in all primary outcomes, suggesting that such counseling may be effectively and efficiently delivered via telephone to increase access and decrease costs [59].

Genetic testing for cancer predisposition requires informed consent that should include pre-test education and counseling concerning the risks, benefits and limitations of testing, including the implications of both positive and negative genetic test results. Early referral at the time of cancer diagnosis may allow for use of the genetic information in treatment planning (e.g., consideration of bilateral mastectomy for breast cancer treatment or clinical trials with PARP-inhibitors for ovarian cancer). Pre-test counseling should also include education on the limitations of current genetic testing technology including the risks of false negative results, as well as the uncertainties associated with genetic variants of unknown significance. Individuals considering genetic testing should be aware that the potential risks of genetic testing include psychological stress and changes to family dynamics. Risks may also include the potential for discrimination in health insurance or employment, but there is little evidence that this has actually occurred to date [60,61]. Additionally, while legal protection against discrimination is not complete, the following provisions do afford some level of protection, including:

A. The Health Insurance Portability and Accountability Act (HIPAA, 1996) specifically stating that genetic information in the absence of a current diagnosis of illness did not constitute a pre-existing condition [http://www.dol.gov/ebsa/facts/fact_consumer_hipaa.html].
B. Executive Order 13145 to Prohibit Discrimination in Federal Employment Based on Genetic Information Feb 2000 - prohibited agencies employed by the federal government from obtaining genetic information about existing employees and from federal job applicants.
C. The Genetic Information Nondiscrimination Act, May 21, 2008, prohibited group health plans from denying coverage to a healthy individual or charging higher premiums based solely on a genetic predisposition to developing a disease in the future.

Genetic assessment for Lynch, in contrast to HBOC, may be performed first through tumor testing. Immunohistochemistry for the four most common mismatch repair genes is a relatively inexpensive test and is available through most pathology laboratories. Loss of mismatch repair proteins can direct targeted germline genetic testing. Testing for microsatellite instability involves comparing normal and tumor tissues from a patient with a potential Lynch syndrome associated cancer.

Post-test counseling should include education on risk-reduction strategies. Genetic testing should be performed by individuals with expertise in cancer genetics, and sufficient training and knowledge to adequately counsel patients. It should be noted that when evaluating a family for possible transmission of a deleterious mutation, it is usually most efficient to start by testing an affected individual. It is also

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**Table 1**

<table>
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<th>Women AFFECTED with:</th>
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<tr>
<td>• High grade Epithelial ovarian/tubal/peritoneal cancer</td>
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<tr>
<td>• Breast cancer ≤ 45 years</td>
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<tr>
<td>• Breast cancer with close relative(a) with breast cancer ≤ 50 years or close relative(a) with epithelial ovarian/tubal/peritoneal cancer at any age</td>
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<tr>
<td>• Breast cancer ≤ 50 years with a limited family history</td>
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<tr>
<td>• Breast cancer with ≥ 2 close relatives(b) with breast cancer at any age</td>
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<tr>
<td>• Breast cancer with ≥ 2 close relatives(b) with pancreatic cancer, aggressive prostate cancer (Gleason score ≥ 7)</td>
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<tr>
<td>• Two breast primaries, with the first diagnosed prior to age 50.</td>
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<tr>
<td>• Triple negative breast cancer ≤ 60 years</td>
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<tr>
<td>• With breast cancer and Ashkenazi Jewish ancestry</td>
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<tr>
<td>• Pancreatic cancer with ≥ 2 close relatives(a) with breast, ovarian/tubal/peritoneal, pancreatic, or aggressive prostate cancer (Gleason score ≥ 7)</td>
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<th>Women UNAFFECTED with, but with:</th>
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<tr>
<td>• A first degree or several close relatives that meet one of the above criteria</td>
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<tr>
<td>• A close relative(b) carrying a known BRCA1 or BRCA2 mutation</td>
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<tr>
<td>• A close relative with male breast cancer</td>
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\(a\) Invasive and ductal carcinoma in situ breast cancers.

\(b\) Close relative is defined as a first degree (parent, sibling, offspring), second degree (grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling) or third degree (first cousin, great-grandparent or great-grandchild) relative.

\(c\) Limited family history includes fewer than 2 first- or second-degree female relatives of female relatives surviving beyond 45 years.

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**Table 2**

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<th>Patients with an increased likelihood of Lynch syndrome and for whom genetic assessment is recommended.</th>
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<tr>
<td>• Patients with endometrial or colorectal cancer with evidence of microsatellite instability or loss of a DNA mismatch repair protein (MLH1, MSH2, MSH6, PMS2) on immunohistochemistry.</td>
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<tr>
<td>• Patients with a first-degree relative(a) affected with endometrial or colorectal cancer who was either diagnosed before age 60 years or who is identified to be at risk for Lynch syndrome by a systematic clinical screen that incorporates a focused personal and medical history [58].</td>
</tr>
<tr>
<td>• Patients with a first or second degree relative(a) with a known mutation in a mismatch repair gene.</td>
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\(a\) First degree relatives are parents, siblings and Children. Second degree relatives are aunts, uncles, nieces, nephews, grandparents and grandchildren.
important to remember that family histories change over time and should be reassessed regularly.

Even in families with inherited cancer susceptibility as a result of HBOC or Lynch, the risk of developing breast, ovarian, endometrial or colon cancer in a woman under age 21 is very low, and the discovery of a mutation associated with one of these syndromes would change the management of very few women in this age group. Therefore, in light of the potential negative consequences of genetic testing, the SGO does not recommend genetic testing of women under age 21 for HBOC or Lynch in the absence of a family history of extremely early-onset cancer. We acknowledge that the NCCN recommends that colonoscopy should start at age 20.

While results of genetic testing may have important implications for a patient's relatives, a physician's principal responsibility is to the individual patient in his or her care. However, patients should be strongly encouraged and provided resources to help them share genetic test results with appropriate family members for whom this information could provide important guidance.

Conflict of interest statement
No potential conflicts of interest were disclosed.

References


