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SGO Committee Statement

Society of Gynecologic Oncologists Education Committee Statement on Risk Assessment for Inherited Gynecologic Cancer Predispositions☆

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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 ovarian cancer. Similarly, women with mutations in the DNA mismatch repair genes, *MLH1, MSH2* or *MSH6*, associated with the Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome, have up to a 40–60% lifetime risk of both endometrial and colorectal cancer as well as a 9–12% lifetime risk of ovarian cancer. Genetic risk assessment enables physicians to provide individualized evaluation of the likelihood of having one of these gynecologic cancer predisposition syndromes, as well 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. Hereditary cancer risk assessment is a *process* that includes assessment of risk, 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 hereditary cancer risk assessment for Hereditary Breast/Ovarian Cancer and the Lynch/Hereditary Non-Polyposis Colorectal Cancer syndrome.

Commentary

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 colorectal cancers [5–11].

☆ This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

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Women with mutations in the *BRCA1* cancer susceptibility gene associated with Hereditary Breast/Ovarian Cancer (HBOC) have a 65–85% risk for breast cancer and a 39–46% risk for ovarian cancer by age 70 [12–14]. Similarly, women with mutations in *BRCA2* have risks of breast and ovarian cancer by age 70 of approximately 45–85% and 10–27%, respectively [12–14]. Women with Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome, caused by mutations in DNA mismatch-repair genes (*MLH1*, *MSH2* or *MSH6*), have risks for endometrial and ovarian cancer by age 70 of approximately 42–60% and 9–12%, respectively [15,16]. Women with HNPCC also have a 40–60% lifetime risk of colorectal cancer. Genetic risk assessment for these hereditary cancer syndromes enables physicians to provide individualized and quantified assessment of risk, as well as options for tailored screening and prevention strategies that may reduce morbidity from these hereditary processes. Strategies that have been demonstrated to improve outcomes in individuals at inherited risk include breast screening with magnetic resonance imaging (MRI), [17,18] colorectal cancer screening with colonoscopy [19] and prophylactic surgery. [20–23]. Given clear evidence demonstrating that risk-reducing interventions can alter the natural history of these inherited predispositions, the Society of Gynecologic Oncologists (SGO) is committed to encourage the medical community to identify women who may benefit from hereditary cancer risk assessment.

It is important to emphasize that hereditary cancer risk assessment is a *process* that:

- Includes assessment of risk, education and counseling;
- Is conducted by a physician, genetic counselor or other provider with expertise in cancer genetics;
- May include genetic testing if desired after appropriate counseling and consent has been obtained.

This commentary provides guidance to physicians and other health professionals in the identification of patients who may benefit from hereditary cancer risk assessment for breast, ovarian and endometrial cancer predisposition associated with the Hereditary Breast/Ovarian Cancer and Lynch/Hereditary Non-Polyposis Colorectal Cancer syndromes.

These guidelines were developed through a series of face to face meetings and conference calls of the SGO Education Resource Panel for Hereditary Cancers. 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 approved by the panel membership and the Executive Committee of the Society of Gynecologic Oncologists.

Given the potential impact on clinical care for both patients as well as their close family members, the SGO Education Resource Panel for Hereditary Cancers believes that individuals with a personal risk of having an inherited predisposition to

Table 1
Patients with greater than approximately 20–25% chance of having an inherited predisposition to breast and ovarian cancer and for whom genetic risk assessment is recommended

- Women with a personal history of both breast and ovarian* cancer
- Women with ovarian cancer* and a close relative† with breast cancer at ≤50 years or ovarian cancer at any age
- Women with ovarian cancer* at any age who are of Ashkenazi Jewish ancestry
- Women with breast cancer at ≤50 years and a close relative† with ovarian* or male breast cancer at any age.
- Women of Ashkenazi Jewish ancestry and breast cancer at ≤40 years
- Women with a first or second degree relative with a known *BRCA1* or *BRCA2* mutation

* Peritoneal and fallopian tube cancers should be considered as part of the spectrum of the Hereditary Breast/Ovarian Cancer syndrome.

† Close relative is defined as a first, second or third degree relative (ie. mother, sister, daughter, aunt, niece, grandmother, granddaughter, first cousin, great grandmother, great aunt).

Table 2
Patients with greater than approximately 5–10% chance of having an inherited predisposition to breast and ovarian cancer and for whom genetic risk assessment may be helpful*

- Women with breast cancer at ≤40 years
- Women with bilateral breast cancer (particularly if the first cancer was at ≤50 years)
- Women with breast cancer at ≤50 years and a close relative† with breast cancer at ≤50 years
- Women of Ashkenazi Jewish ancestry with breast cancer at ≤50 years
- Women with breast or ovarian cancer at any age and two or more close relatives† with breast cancer at any age (particularly if at least one breast cancer was at ≤50 years)
- Unaffected women with a first or second degree relative that meets one of the above criteria

* In families with a paucity of female relatives in either lineage, it may also be reasonable to consider genetic risk assessment even in the setting of either an isolated case of breast cancer at ≤50 years or an isolated case of ovarian, fallopian tube or peritoneal cancer at any age.

† Close relative is defined as a first, second or third degree relative (ie. mother, sister, daughter, aunt, niece, grandmother, granddaughter, first cousin, great grandmother, great aunt).

Table 3
Patients with greater than approximately 20–25% chance of having an inherited predisposition to endometrial, colorectal and related cancers and for whom genetic risk assessment is recommended

- Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria [30] as listed below:
  - At least 3 relatives with a Lynch/HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis) in one lineage;
  - One affected individual should be a first degree relative of the other two;
  - At least 2 successive generations should be affected;
  - At least 1 HNPCC-associated cancer should be diagnosed before age 50.
- Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50
- Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50
- Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (i.e. microsatellite instability (MSI) or immunohistochemical loss of expression of MLH1, MSH2, MSH6 or PMS2)
- Patients with a first or second degree relative with a known mismatch repair gene mutation

Table 4
Patients with greater than approximately 5–10% chance of having an inherited predisposition to endometrial, colorectal and related cancers and for whom genetic risk assessment may be helpful

- Patients with endometrial or colorectal cancer diagnosed prior to age 50
- Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/HNPCC-associated tumor* at any age
- Patients with endometrial or colorectal cancer and a first degree relative with a Lynch/HNPCC-associated tumor* diagnosed prior to age 50
- Patients with colorectal or endometrial cancer diagnosed at any age with two or more first or second degree relatives† with Lynch/HNPCC-associated tumors*, regardless of age
- Patients with a first or second degree relative† that meets the above criteria

* Lynch/HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel.

† First and second degree relatives are parents, siblings, aunts, uncles, nieces, nephews, grandparents and grandchildren.

cancer of greater than approximately 20–25% *should* undergo genetic risk assessment. The SGO Education Resource Panel for Hereditary Cancers also believes that it is reasonable to offer genetic risk assessment to any individual with greater than approximately 5–10% chance of having an inherited predisposition to cancer. While the specific criteria outlined in Tables 1–4 identify individuals that generally meet these thresholds, there are some patients who do not meet one of the specific criteria listed who may still benefit from genetic risk assessment. 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 [24,25];
- Hysterectomy and/or oophorectomy at a young age in multiple family members as this might mask a hereditary gynecologic cancer predisposition [26];
- Presence of adoption in the lineage.

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. 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 [27,28]. Additionally, while legal protection against discrimination is not complete, the Health Insurance and Portability and Accountability Act (HIPAA) of 1996 did prohibit a genetic test result in the absence of symptoms from being classified as a preexisting condition [29].

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 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/HNPCC, 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, and in light of the potential negative consequences of genetic testing, the SGO Education Resource Panel for Hereditary Cancers does not recommend genetic testing of women under age 21 for HBOC or Lynch/HNPCC in the absence of a family history of extremely early-onset cancer. While results of genetic testing may have important implications for a patient's relatives, we believe that a physician's principal responsibility is to the individual patient in their care. We also believe, however, that patients should be strongly encouraged to share genetic test results with appropriate family members for whom this information could provide important guidance.

Conflict of interest statement
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