



Society of Gynecologic Oncology

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2016 GENETICS TOOLKIT

A Collaboration of the Society of Gynecologic Oncology,
American College of Obstetricians and Gynecologists,
National Society of Genetic Counselors, Bright Pink and
Facing Our Risk of Cancer Empowered (FORCE)



The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS



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The purpose of this toolkit is to provide access to critical and practical information to health care providers, our patients, their families, and anyone interested in gaining a deeper understanding of the role of genetics in gynecologic cancers. As this is a collaborative effort of several societies, our members and supporters cover a wide audience that includes gynecologic oncologists, medical oncologists, genetic counselors, obstetrician gynecologists, general practitioners, and the lay community.

The toolkit is comprised of specific case studies telling an individual woman's story to illustrate common questions and challenges faced by practitioners and their patients. Key points are illuminated from each organization's perspective. Each case history includes references, national guidelines and, society statements. A "General Resources" section includes useful tools and websites of interest.

Case 1: *BRCA1*- and *BRCA2*-related ovarian cancer

Janet is 58 years old and has a recent history of abdominal pain and bloating. Her primary care physician obtained a CT scan of her abdomen and pelvis. The scan showed a pelvic mass, thickening of the omentum (fatty apron that hangs from the colon), and fluid accumulation (ascites). Janet was referred to a gynecologic oncologist due to the concern for a gynecologic malignancy. Her gynecologic oncologist performed surgery to remove the uterus, fallopian tubes, and ovaries, as well as to remove the visible tumor on other surfaces and staging her cancer. The final pathology report diagnosed stage III high-grade serous ovarian cancer.

After recovering from her surgery, Janet started the adjuvant chemotherapy that her oncologist recommended. She was surprised that her oncologist also recommended that she undergo genetic counseling and testing. She did not think she was at risk for an inherited susceptibility to cancer since she has no family history of breast, colon, or ovarian cancer. She has concerns about the cost of genetic testing and the impact that it might have on her insurance status. Her 30-year-old daughter, Susan, has been having a hard time accepting Janet's cancer diagnosis. Janet worries that a result showing an inherited mutation might be too overwhelming for Susan.

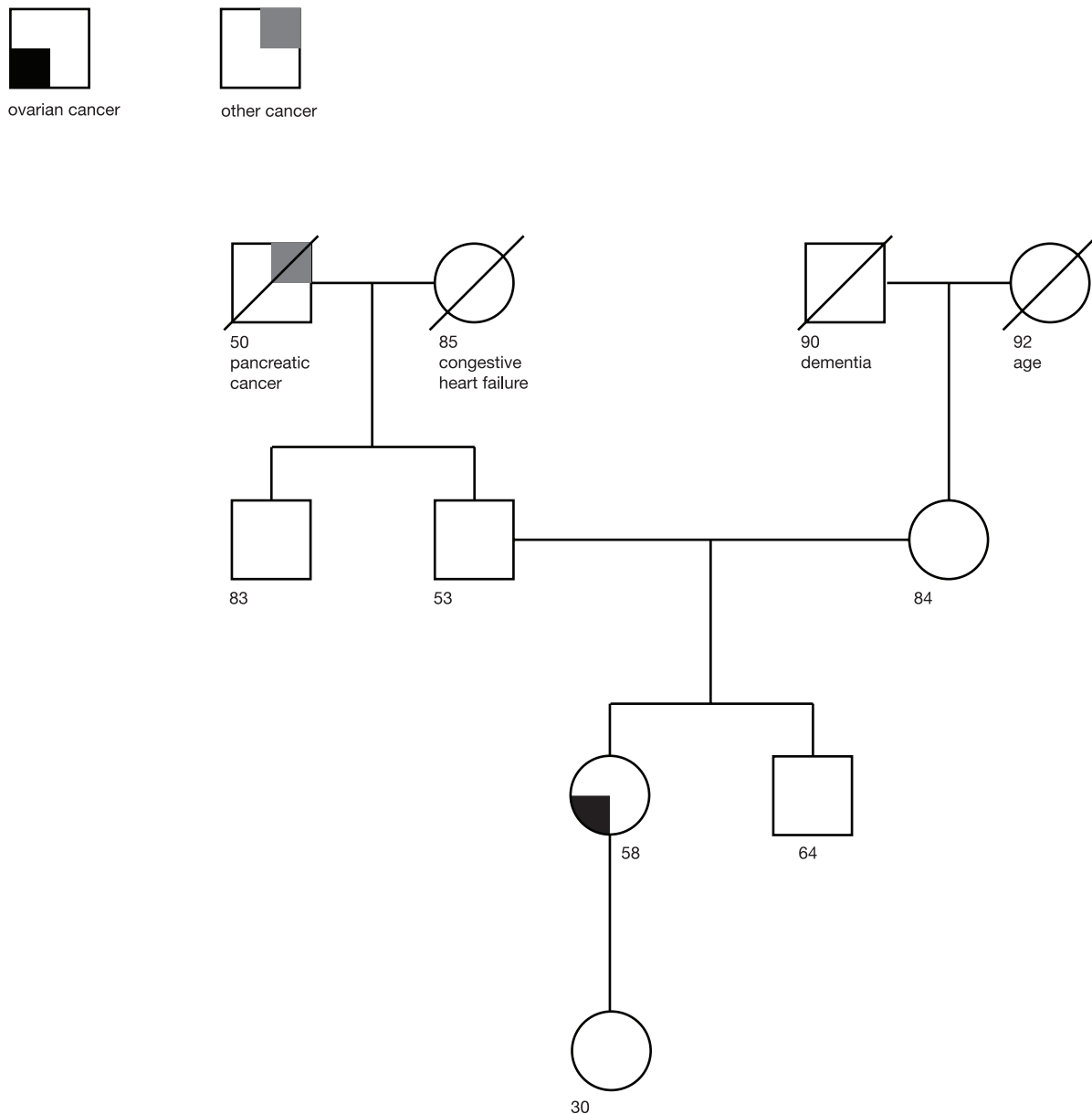


Fig. 1.

Janet's pedigree, or family history tree. Often inherited patterns will show multiple family members with cancer, cancer at young ages and cancer in several generations but one third (about 30%) of women who have ovarian cancer and an inherited genetic risk do not have a strong family history.

Questions

Why is Janet's oncologist recommending genetic counseling and testing for her?

All women with epithelial ovarian, fallopian tube, and primary peritoneal cancer have been recommended to undergo genetic counseling and testing since the National Comprehensive Cancer Network (NCCN) issued its 2011 guidelines. The Society of Gynecologic Oncology (SGO) has endorsed that recommendation. It is based on data that about 20 percent of women with these cancers carry an inherited mutation in *BRCA1*, *BRCA2*, *MSH2*, *MLH1*, *MSH6*, *PMS2*, *EPCAM*, *BRIP1*, *RAD51C*, *RAD51D*, *PALB2*, and/or *BARD1*. Increased hereditary risk is associated with young age at diagnosis, family history of breast and/or ovarian cancer, and some ethnicities such as Ashkenazi Jewish ancestry. These factors do not need to be present in order to make testing reasonable since at least one third of women with hereditary ovarian cancer have none of these risk factors. All histologic types of invasive (not borderline) epithelial ovarian cancers should prompt consideration for referral to genetic counseling and testing. Mucinous ovarian cancer represents a rare exception since it has not been routinely shown to be part of hereditary breast and ovarian cancer or Lynch syndromes. Genes that increase the risk of breast cancer as well as ovarian cancer are part of hereditary breast and ovarian cancer (HBOC) syndrome. Those genes that increase the risk of colon, endometrial and ovarian cancer are associated with Lynch syndrome.

What types of genetic tests are available to Janet?

Traditionally, genetic testing has been performed one or two genes at a time, starting with the gene(s) considered most likely to be involved based on the patient's personal and family history. The testing looks for germline changes (mutations) in genes, meaning that they are in every cell and can be passed on to children. This process can be expensive and time-consuming if multiple genes could be involved. Recently, multi-gene panel tests have been developed that include anywhere from a handful to several dozen cancer predisposition genes. These panels have the advantage of testing for many potential gene mutations simultaneously at a lower cost than traditional testing. Because so many genes in a panel are being investigated, however, there is also a higher likelihood of diagnosing a variant of uncertain significance (VUS), which is a genetic change without any clear association to a health problem. Changes in a gene that are known to be associated with a health problem like cancer are called deleterious mutations or pathogenic variants.

Clinical recommendations like enhanced cancer screening or risk-reducing surgery are reserved for those individuals who are found to have a deleterious mutation or who have a strong family cancer history, because most VUS are ultimately found *not* to be associated with health problems and medical decisions should not be based on the presence of a VUS. The decision to pursue gene-by-gene testing versus panel testing is a complex one that benefits from discussion with a genetics professional. In addition to germline testing, patients may also benefit from having the tumor itself tested for mutations. Mutations that occur in the tumor are called somatic mutations and cannot be passed through the family (unlike germline mutations). Knowledge of either germline or somatic mutations may help direct treatment.

How might the genetic test results affect Janet's treatment? Would they affect her eligibility for clinical trials?

Janet's treatment might be affected in several ways if she is found to have a gene mutation. If she was found to have a *BRCA1* or *BRCA2* mutation, for example, and her ovarian cancer goes into remission, she might choose to receive enhanced breast cancer screening. Survival from ovarian cancer is improved in women who have a *BRCA1* or *BRCA2* mutation compared with those who do not have a mutation, and *BRCA1*- and *BRCA2*-related ovarian cancer may be more sensitive to platinum chemotherapy. This may affect treatment options for her. If her ovarian cancer recurs, she might be eligible for treatment with a class of drugs called PARP inhibitors that are particularly effective in women with *BRCA1* and *BRCA2* mutations. Currently, the PARP inhibitor, olaparib, is FDA-approved in the United States for women with recurrence of ovarian cancer after three previous lines of therapy if they carry a germline *BRCA1* or *BRCA2* mutation. However, clinical trials with PARP inhibitors might be available for women in other clinical settings, such as mutations in genes other than *BRCA1* and *BRCA2*, fewer prior treatment regimens, or somatic mutations in their tumor rather than in the germline.

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Case 2: Daughter of *BRCA1* mutation carrier

Susan is Janet's daughter. Susan is now 34 years old and is trying to get pregnant. She has unexplained infertility and is planning to undergo her first cycle of in vitro fertilization (IVF) with her husband next month. Her mother, Janet, was recently diagnosed with ovarian cancer at age 58, and Janet has undergone genetic testing and has a mutation in *BRCA1*. Susan is tearful while discussing her mother's cancer, and is questioning whether she should move forward with IVF both due to fear of her own risk of cancer, and the possibility that her future children could be at increased risk.

She and her husband are self-employed and their insurance does not cover her fertility treatments, so she is not sure she can afford genetic testing. She also worries that she might lose her insurance if she is found to carry a gene mutation that increases her risk of cancer.

Questions

What is the potential psychological impact of undergoing genetic testing?

Although genetic testing can be stressful for patients in the short term, most patients have a sense of relief in knowing their genetic status and can then move forward with their long-term health planning based on additional information about their personal risk level. For those patients who test negative for a mutation that is known to be in the family, there is often significant relief of stress that they do not carry the elevated risk that caused cancer in their family. For those who test positive, there is opportunity to establish a risk-reduction plan moving forward with renewed certainty about the utility of such a plan. Taking action to modify a known risk can feel more empowering than the sense that cancer "might be coming" at any time.

While genetic testing has the potential to reduce anxiety by giving a concrete result, it is important to note that genetic counseling does not infer that genetic testing must be done. Some patients are not ready to move forward with testing immediately, and genetic counseling gives them information to use at any place in their process of coming to terms with their hereditary risk.

Is genetic counseling and testing typically covered by insurance? What is the typical cost of genetic testing?

Genetic counseling and testing for individuals at risk for *BRCA* mutations are considered preventive services under the Affordable Care Act, and thus are a covered benefit for qualifying patients with ACA health plans. Private insurers typically follow similar guidelines; however, plans can vary in their requirements and qualifications for testing (e.g., number of affected relatives).

The number of companies offering testing has increased over the last few years, so the price of testing varies by company. Without insurance coverage, the cost of a full *BRCA1* and *BRCA2* analysis varies from \$249 to \$3,500 depending on the company conducting the testing. Many laboratories offer panel testing for multiple genes that have been associated with breast and/or ovarian cancer risk, rather than *BRCA1* and *BRCA2* alone. While comprehensive testing is required if a patient is the first in their family to undergo testing, a single site analysis (test that looks for the family's known mutation) can be done for relatives of a patient who knows their specific mutation, frequently at lower cost than for a panel test. Since Susan's mother has a known mutation, Susan could be tested for the single site mutation carried by her mother.

It is important to note that *BRCA1* and *BRCA2* are not the only gene mutations that increase the risk of ovarian cancer, so it is crucial that this patient's family history be reviewed by a genetic counselor who can determine whether Susan may be at risk for other mutations. For example, Susan could also have inherited risk from her dad which would be missed if she is only tested for her mom's mutation.

If Susan tests positive for a *BRCA1* or *BRCA2* mutation, what surveillance and risk-reduction strategies are recommended for her? Is her fertility altered by a mutation?

If Susan tests positive for a *BRCA1* and *BRCA2* mutation, heightened surveillance and several risk reduction options are available for her. For her breast cancer risk, increased surveillance is recommended, including annual magnetic resonance imaging (MRI) and mammography. Such screening can detect cancer early but does not prevent cancer. She would also have opportunity to reduce the risk of breast cancer by up 97 percent by opting for a risk reducing mastectomy (surgical risk reduction). Women with *BRCA2* mutations who more commonly develop estrogen receptor positive breast cancer can be offered a type of chemoprevention drug called selective estrogen receptor modulator (SERM) which are associated with breast cancer risk reduction of up to 50 percent.

For her ovarian risk, she could reduce her risk by using oral contraceptives; however, surgical risk reduction with bilateral salpingo-oophorectomy (removal of the fallopian tubes and both ovaries), is recommended after childbearing is complete. Removing tubes and ovaries will reduce the risk of ovarian, fallopian tube and peritoneal cancer by more than 80% and the risk of breast cancer by 50%. There is growing interest in earlier salpingectomies (removal of the fallopian tubes) with delayed oophorectomy (ovary removal) in order to delay the onset of menopause; however, clinical trials using this strategy of salpingectomy and delayed oophorectomy are not yet completed, so the degree of risk reduction is not known. Patients with a known *BRCA1* mutation should consider removing tubes and ovaries after childbearing and between ages 35 and 40. For women with *BRCA2* mutations, the risk of ovarian cancer occurs later; they may delay removal of tubes and ovaries to 40- 45 years of age if they have already undergone a bilateral mastectomy and minimized their breast cancer risk. Estrogen replacement therapy is safe and reasonable if breast cancer has not been previously diagnosed. Removal of the uterus along with the tubes and ovaries is sometimes recommended based on personal factors discussed in Case 3.

Is her fertility altered by a mutation? Does IVF increase her risk of ovarian cancer?

Fertility treatment does not in itself increase the risk of cancer, but patients who are infertile are at greater risk of ovarian cancer. In addition to having an elevated risk of ovarian cancer, infertile *BRCA1* and *BRCA2* mutation carriers may have decreased ovarian reserve and can prove more difficult to stimulate through IVF. However, if fertilization is successful, preimplantation genetic diagnosis (PGD) can be utilized to select embryos without the mutation and avoiding passing on the mutation to offspring if that is a priority to the parents. Some studies have suggested that women with *BRCA1* mutations may go through menopause a year earlier than the general population but a decrease in fertility has not been proven.

It should also be noted that *BRCA2* gene mutations can be associated with a rare disorder called Fanconi anemia if a person inherits a *BRCA2* mutation from each parent. For this reason, careful attention should be given to the family history of *BRCA2* mutation-carriers' partners when family planning is being considered. It is sometimes appropriate to offer *BRCA2* gene testing (at a minimum) to the mutation carrier's partner in this situation.

What protections are in place against insurance discrimination?

The Genetic Information Nondiscrimination Act (GINA) is a federal law that protects against discrimination by employers or health insurers based on genetic information. GINA does not cover disability or life insurance. These insurers do often request information about family health history, so patients considering genetic testing could potentially face difficulty obtaining disability or life insurance whether they have tested or not. Some plans will offer coverage in the face of familial cancer risk, but place a rider on disability or death from a cancer common to a family. Riders are often required for a period of time after surgeries as well, so patients may be excluded from full coverage until several years after a risk-reducing surgery. Given the potential implications, some individuals choose to obtain disability or life insurance prior to testing.

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Case 3: Risk-reducing salpingo-oophorectomy

Susan is now 40 years of age, with a feisty four year old and has decided to undergo a risk-reducing salpingo-oophorectomy (RRSO). Susan's gynecologist performs a laparoscopic RRSO. After surgery, Susan meets with her doctor to review the pathology report, which shows some atypical cells in the fallopian tubes, called serous tubal intraepithelial carcinoma (STIC).

Questions

Are any special procedures part of a (RRSO) surgery?

RRSO is usually performed as a minimally invasive (laparoscopic) surgery that takes approximately 60 to 90 minutes. This outpatient surgery is usually performed with several small incisions. All ovarian tissue and as much fallopian tube as possible is carefully removed from its junction with the uterus. The abdomen is thoroughly inspected and a pelvic wash called cytology is performed. The ovaries and tubes are then cut into very small sections (2 to 3 mm) so that each section is carefully examined by the pathologist for early cancer or pre-cancer. It is very important that this special pathology is done in order to detect very tiny cancers that could already be present. The entire fallopian tube must be examined in careful detail as many of the pre-cancer and early cancer changes are found in the fallopian tube.

What is the benefit of risk reducing (RRSO) surgery?

RRSO prevents approximately 80 percent of ovarian/fallopian tube and peritoneal cancer in women who carry *BRCA1* and *BRCA2* mutations. Current guidelines recommend RRSO for women between the ages of 35 and 40, although delaying until mid-forties in women with *BRCA2* mutations may be considered because the incidence of ovarian cancer is approximately 1 percent for women under age 50. Breast cancer risk may also be reduced by premenopausal RRSO. One study has shown that RRSO surgery also reduces death from all causes in women with *BRCA1* and *BRCA2* mutations as well as deaths specifically from breast and ovarian cancer. One caution is that women can still get primary peritoneal carcinoma, an ovarian-like cancer, after RRSO, however the risk is very low, particularly when the ovaries and fallopian tubes were carefully examined for early cancers.

Should hysterectomy be performed along with RRSO?

Generally, it has been suggested that patients with *BRCA1* and *BRCA2* mutations are not at increased risk of developing uterine carcinoma, although data have suggested a small increased risk of serous endometrial cancer. Another potential advantage of hysterectomy performed at the time of risk-reducing surgery is to facilitate postoperative hormonal therapy; if hysterectomy were performed, only estrogen would be needed, which confers lower risk of hormone therapy complications compared to combined therapy with estrogen and progestin. Some women choose hysterectomy because they are on tamoxifen for breast cancer risk reduction, and tamoxifen is associated with an increased uterine cancer risk. Still others may have other gynecologic reasons for desiring hysterectomy, such as fibroids or abnormal Pap smears. An argument against hysterectomy is a small increase in recovery time and surgical complications associated with the addition of hysterectomy to salpingo-oophorectomy. Generally, the decision to include hysterectomy with RRSO in *BRCA1* and *BRCA2* mutation carriers should be based on a full discussion of risks and potential benefits in shared decision-making between the patient and her surgeon.

What is the significance of serous tubal intraepithelial carcinoma (STIC)?

STIC was first identified in the fallopian tube specimens removed from women with a *BRCA1* or *BRCA2* mutation. It comprises cancer cells that are confined to the innermost layer of the fallopian tube, called the endothelium, and have not yet invaded to deeper tissues as a true invasive carcinoma would. They are almost always found on the fimbriae, the end of the fallopian tube furthest from the uterus.

STIC or invasive cancers are identified in 4-10% of women with *BRCA1* and *BRCA2* mutations when complete serial sectioning of the fallopian tubes is performed at RRSO. These pre-invasive and invasive lesions are more commonly found in women with *BRCA1* mutations over age 45 at the time of surgery.

The management of women in whom only STIC but no invasive cancer is identified is not well established. The risk that a STIC will develop into an invasive carcinoma in the tube or spread to the ovary is not known. Pelvic washings are sometimes positive for abnormal cells in women in whom STIC has been identified, raising the possibility that a small cancer may have already spread to the peritoneal surfaces.

Based on an uncertain risk of developing carcinoma in the future, management protocols for women with STIC have ranged from surveillance to surgical staging and consideration of chemotherapy. CA-125 levels are usually normal but may be helpful to raise suspicion of more extensive disease. Each patient with STIC should discuss her options with her gynecologic oncologist.

What is the association of fallopian tube cancer with *BRCA1* and *BRCA2* mutations?

When STIC and invasive fallopian tube cancer were seen in RRSO specimens from women with *BRCA1* and *BRCA2* mutations, we realized that the fallopian tube, rather than the ovary, might be the originating site of many pelvic serous cancer cases. This has changed the thinking about the prevention of “ovarian” cancer to include an emphasis on the fallopian tube. The increased risk of ovarian cancer associated with *BRCA1* and *BRCA2* mutations is more accurately stated as an increased risk of pelvic serous cancers, including fallopian tube, ovarian and peritoneal cancers.

Are there surgical alternatives to RRSO?

Tubal ligation has been associated with some risk reduction of ovarian cancer. More recently, risk-reducing salpingectomy has been suggested as a bridge to delayed oophorectomy in young women with *BRCA1* and *BRCA2* mutations who desire risk reduction that avoids menopause. Delaying oophorectomy, however, negates the risk reduction for breast cancer in these women. In addition, cases of pelvic cancer arising in the ovaries would not be prevented. Salpingectomy instead of BSO has not yet been fully evaluated as to safety or effectiveness in women at high risk of ovarian cancer. Observational trials are ongoing in the United States and Europe to collect more information about this alternative

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Case 4: Health outcomes after risk-reducing salpingo-oophorectomy

Still at age 40, Susan (see Case 3) has undergone a laparoscopic RRSO for *BRCA1* and *BRCA2* mutations. She is concerned about health outcomes, including menopause and quality of life after surgery. She wonders what follow-up she should have after the surgery to manage her cancer risk.

Questions

What are the potential consequences of premature menopause due to the surgery?

The typical age for menopause in the U.S. is about 51 years. While removing tubes and ovaries in mutation carriers at a younger age is very important to prevent ovarian cancer, it does cause early menopause. Premature menopause is associated with several health risks, including early onset of cardiovascular disease and osteoporosis. Other long-term health issues include an increased risk of cognitive impairment and dementia, particularly with younger age at oophorectomy. Parkinsonism, anxiety, and psychosexual dysfunction also constitute significant risks. The sudden menopause that occurs with surgical removal of the ovaries can cause bothersome and persistent symptoms as well as the negative impact on long-term health. Non-hormonal prevention measures such as a healthy diet, appropriate calcium and vitamin D intake, and weight-bearing exercise can improve bone and cardiovascular health. Maintaining a healthy weight, limiting alcohol intake, avoiding tobacco, getting adequate sleep, and managing stress also improve overall health and decrease cancer risk.

Is hormone replacement therapy an option for Susan?

The results of the Women's Health Initiative and the Nurses' Health study have raised concern about whether hormone replacement therapy is an option after RRSO. However, the patients in the WHI were women who underwent spontaneous menopause in their 50s and then took additional hormone therapy. These women in WHI are a vastly different population than *BRCA1* and *BRCA2* mutation carriers, who typically make the decision about RRSO, a decade earlier, in their 30s and 40s, before they have entered natural menopause. Therefore, conclusions from the WHI are not applicable to early surgical menopause.

In women who have not had a hormone receptor-positive breast cancer, no study has shown an increased risk of breast cancer associated with hormone therapy in women who have undergone RRSO prior to menopause. In addition, one study conducted in patients with *BRCA1* and *BRCA2* mutations demonstrated that short-term use of hormone therapy did not negate the protective effect of RRSO on risk of subsequent breast cancer; the majority of these patients were receiving estrogen alone, not combined estrogen and progestin therapy.

Even if a woman chooses not to take systemic hormone therapy, local estrogen treatment to the vagina can help with dyspareunia (painful intercourse), vaginal dryness, and other urogenital symptoms. Vaginal estrogen has not been shown to increase the risk for breast cancer since its effect is largely limited to the local tissues. Such treatment, however, does not help with other menopausal effects, such as heart disease, osteoporosis, or hot flashes.

What can Susan do to address sexuality-related concerns?

Women who undergo RRSO are at risk of developing symptoms that affect sexual function, including decreased desire, vaginal atrophy, and dyspareunia. Body image may be particularly impacted in women who have undergone risk-reducing mastectomies. Hormone therapy, when appropriate, may help but may not necessarily alleviate all symptoms. It is important that both providers and patients are aware of this phenomenon, such that patients can be realistically counseled about these outcomes and to be prepared to address persistent symptoms. Resources available to women to improve menopausal symptoms are listed below.

What kind of post-RRSO surveillance might be used?

Clearly, RRSO substantially reduces the risk of pelvic serous cancer, with an approximate 80 to 90 percent reduction in risk. Additionally, premenopausal oophorectomy is associated with a 50 percent reduction in breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. A small residual risk for peritoneal cancers remains after RRSO, with more recent estimates at 1 to 2 percent. Risks may be somewhat higher for women who did not have complete serial sectioning done at the time of RRSO. Because we have no effective screening for peritoneal cancer, there is no clearly established recommendation for surveillance following risk-reducing surgery. It is important for the patient and her health care providers to consider this risk for peritoneal cancer if she develops abdominal symptoms such as pain, bloating, early satiety, or nausea and vomiting.

Because of increased risk of cardiovascular disease and osteoporosis in women who undergo early menopause, surveillance with lipid profiles and bone density scans are recommended.

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Case 5: Impact of hereditary breast and ovarian cancer genes on male family members

Rob, the son of Janet (see Case 1), is 32. He and his wife have a 4-year-old daughter and are planning to have additional children soon. After learning about her mother-in-law's diagnosis, his wife asks their family doctor if Rob should undergo genetic testing. Rob's wife would like to know if he has a mutation before becoming pregnant again. She has heard about preimplantation genetic diagnosis and would like to know more about their options for avoiding passing on a mutation to their child. Rob is reluctant to pursue testing; he feels healthy and does not see the benefit of testing.

Questions

Which family members should consider genetic testing first?

The best person to undergo genetic testing in a family with a medical history suggestive of hereditary breast and ovarian cancer (HBOC) is the family member(s) most likely to carry a mutation. This is usually a family member with a cancer diagnosis suggestive of HBOC, such as those with ovarian cancer, young-onset breast cancer, or triple-negative breast cancer. However testing an affected family member is not always possible, especially when those affected by cancer have already passed away.

What is cascade testing?

Cascade testing is the favored approach for testing relatives in a family with an identified mutations that causes hereditary breast and ovarian cancer (HBOC), in which first degree relatives of the proband with the mutation are tested and then additional people are tested that are related to each family member who is found to carry the mutation. Cascade testing is a cost-effective approach to testing because the cost is low and the pre-test probability of identifying a mutation carrier is high.

Should men in families with inherited risk of ovarian and breast cancer consider testing? Is there special surveillance recommended for men?

Men with *BRCA1* and *BRCA2* mutations have an increased cancer risk that is higher than an average man's risk but not as high as the risk for women with *BRCA1* and *BRCA2* mutations. This risk is higher for men with *BRCA2* mutations than *BRCA1* mutations. The cancers associated with mutations include:

- Male breast cancer
- Prostate cancer
- Pancreatic cancer
- Melanoma

NCCN guidelines for risk-management in men with mutations include:

- Breast self-exam training and education starting at age 35 years
- Clinical breast exam, every 12 months, starting at age 35 years
- Starting at age 40 years:
 - Recommend prostate cancer screening for *BRCA2* mutation carriers
 - Consider prostate cancer screening for *BRCA1* mutation carriers

The above recommendations constitute a change from usual medical care and provide justification for testing men for *BRCA1* and *BRCA2* mutations. However, insurance companies do not always pay for testing in men.

What is the role of preimplantation genetic testing in families with *BRCA1* and *BRCA2* mutations?

Preimplantation genetic diagnosis (PGD) can be used to select and implant embryos that do not have a mutation. PGD would require that Rob's wife also undergo in vitro fertilization (IVF). These procedures can be costly and are often not covered by health insurance. Financial assistance programs are available to offset costs. In general, PGD is utilized more commonly for genetic diseases in which outcomes are severe or affected offspring are at risk for disease in childhood, especially if no prevention methods are available, while the risk with *BRCA1* and *BRCA2* mutations is for cancer as an adult, with significant potential for screening and risk reduction.

Case 6: Ambiguous test results and variants

Mary is 33 years old and has just been diagnosed with breast cancer. Her mother has a *BRCA1* mutation, so she assumes she will also test positive for this mutation. To Mary's surprise, she tests negative for the *BRCA1* mutation that her mother carries.

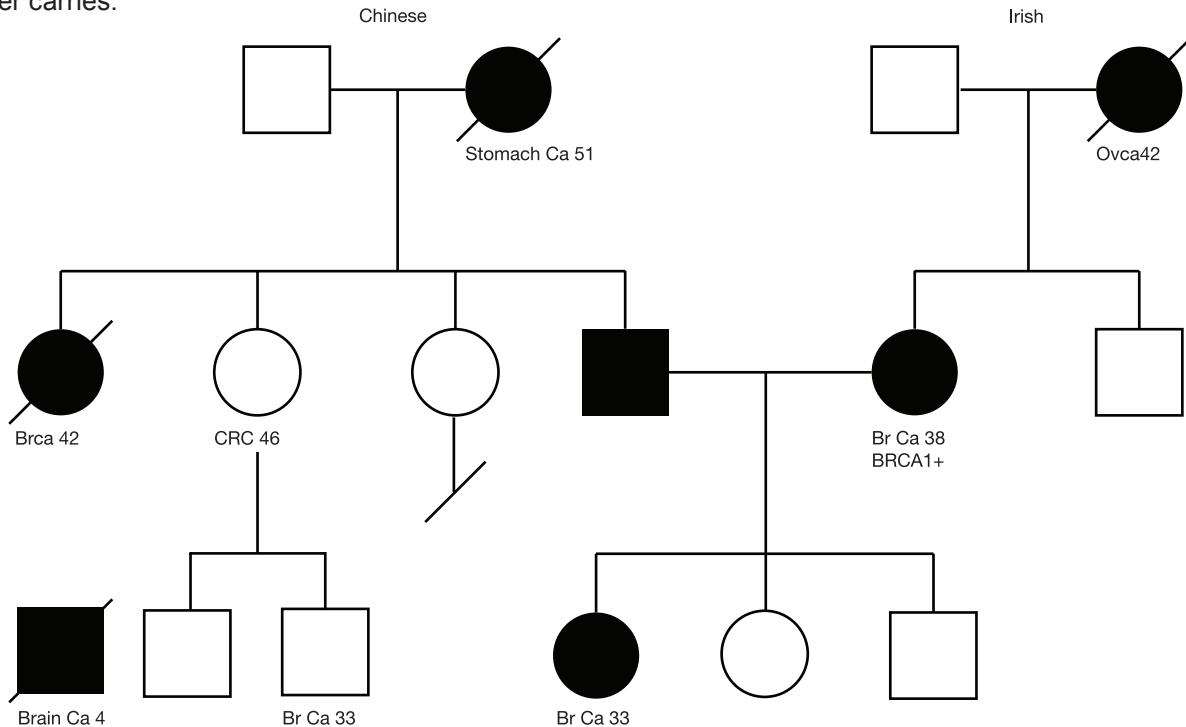


Fig. 1.

A family pedigree that shows multi-generational cancers occurring at young ages, on both the maternal and paternal sides. This patient could have inherited a genetic mutation placing her at increased risk of cancer from either side.

Questions

Should Mary considering further genetic testing?

There are two main reasons that Mary should consider additional genetic testing. One reason is her young age at diagnosis of breast cancer. National Comprehensive Cancer Network guidelines recommend consideration of genetic testing for women diagnosed with breast cancer ≤ 45 years old. A second reason is her strong paternal family history of cancer. Most inherited cancer risk follow an autosomal dominant inheritance pattern, meaning there is a 50-50 chance that an affected parent will pass the mutation to a child of either sex. Therefore, the paternal family history is equally as important as the maternal history for hereditary cancer risk assessment. Mary's paternal family history is suggestive of an inherited risk for cancer.

What type of additional genetic testing should Mary pursue?

Historically, genetic testing has been offered in a sequential manner, gene by gene. This approach can be timely and expensive if there are multiple genes being considered for testing. Recent advances in genetic testing with next generation sequencing make it possible to test multiple genes simultaneously, with lower cost and faster turnaround time for results.

Mary's personal and paternal family history is suggestive of more than one inherited cancer syndrome. At a minimum, complete testing of *BRCA1* and *BRCA2* should be offered. Testing for *TP53* (Li Fraumeni syndrome) should also be considered in women diagnosed with breast cancer under age 31, even in the absence of family history of cancer (1). While it remains unclear whether breast cancer is associated with Lynch syndrome, her father's diagnosis of colon cancer at 46 years of age and her paternal grandmother's diagnosis with stomach cancer raise suspicion for Lynch syndrome.

There are also many other genes that have been implicated in hereditary cancer risk with overlapping cancer types.

Current NCCN guidelines recommend considering a multi-gene panel when more than one gene could explain an inherited cancer syndrome, or when someone tests negative for a specific inherited cancer syndrome but their history remains strongly suggestive of an inherited cancer syndrome. A multi-gene panel would be a reasonable approach to testing for Mary, so that multiple hereditary cancer genes could be assessed at once. Due to the complexities of genetic testing options, medical and psychosocial implications, and results interpretation, genetic testing should be pursued in the context of genetic counseling by a genetics professional.

Mary pursues a multi-gene cancer panel that tests for mutations in 24 genes associated with hereditary cancer risk. She is found to have a variant of uncertain significance (VUS) in the *CHEK2* gene.

If Mary were found to carry a variant of uncertain significance (VUS), what would this mean to Mary and her family members?

Variants of uncertain significance are changes in the sequence of the DNA where there is too little information known about the specific DNA change to classify it as disease causing (pathogenic variant or mutation) or normal variation (benign polymorphism). VUS are more commonly reclassified as benign changes when more information becomes available, but some are eventually considered pathogenic mutations. Various commercial labs report VUS rates that range from 9% to 41% in multi-gene panels.

Mary and her family members should be counseled about future cancer risks based on assessment of the family history of cancer, not the presence of the VUS. The VUS cannot be used to define future cancer risks for Mary, nor for cancer risk management recommendations. If multiple family members affected with cancer carry the VUS, then it is more suggestive of causation, but 50% of first degree relatives will carry the VUS just by chance, so it takes a large family or multiple families to prove the VUS segregates with cancer. Testing unaffected relatives for a VUS is not useful.

Does Mary's multi-gene test result rule out an inherited cancer risk for her and her family members?

Mary's test result does not rule out an inherited risk for cancer for her or her family members. While Mary did not inherit the *BRCA1* mutation that her mother carries and her multi-gene panel test was inconclusive with a *CHEK2* VUS, the fact remains that Mary was diagnosed with breast cancer at a very young age. In addition, she has a paternal family history of cancers that is unexplained and suggestive of inherited risk for cancer. Mary and her family members remain at increased risk for the cancers present in close family members.

It is possible that Mary has an inherited mutation in a different cancer risk gene or a mutation in a targeted gene that was not identified. There may be additional genes associated with hereditary cancer risk that are not yet incorporated into multi-gene panels. Additionally, genetic testing is not 100% sensitive, so mutations may be missed in the targeted genes.

It is also possible that Mary's cancer is due to multifactorial cancer risk, where multiple small, genetic factors she inherited from one or both sides of her family have combined with environmental and/or lifestyle factors to increase her risk for cancer. There is currently no clinical genetic testing for these types of smaller inherited risk factors.

Finally, it cannot be ruled out that Mary has a sporadic breast cancer diagnosis. It may be that her father and other paternal family members have a mutation in an inherited cancer risk gene, but Mary did not inherit it and simply developed a young breast cancer sporadically.

What surveillance is recommended to Mary and her family members?

Mary and her family members should consider cancer risk management options based on the family history of cancer. This may not be explained by the *BRCA1* mutation on the maternal side. This would include colon and breast cancer screening at an earlier age.

Mary should be encouraged to keep in touch with her genetics professional regarding the interpretation of the *CHEK2* VUS and advances in genetic testing. If the *CHEK2* VUS is reclassified in the future to either a benign polymorphism or a pathogenic mutation, that information will benefit both Mary and her family members. She should also update her genetics professional with any changes to her personal or family cancer history as this may alter her family history assessment. As knowledge of inherited cancer risk genes advances, there may be additional genetic testing for Mary to consider in the future.

Her father should seek genetic counseling to consider appropriate genetic testing based on his diagnosis of cancer and family history of cancer (4). If he were found to have an inherited gene mutation, it would be important to verify whether Mary's panel test would have identified that specific mutation, and her siblings could also consider testing for the mutation.

Mary's siblings should seek genetic counseling (4) and consider genetic testing for the known *BRCA1* mutation that their mother has, since they are each at 50% risk to inherit this mutation despite Mary's negative testing for it.

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Case 7: Lynch syndrome

Rachel is a 44-year-old woman with a body mass index (BMI) of 32. She presented with abnormal uterine bleeding to her gynecologist, who performed an endometrial biopsy that indicated endometrial cancer, specifically endometrial adenocarcinoma of endometrioid histology. She was referred to a gynecologic oncologist and underwent a total hysterectomy and bilateral salpingo-oophorectomy. The pathology from this procedure confirmed that she has stage I disease. She required no adjuvant chemotherapy or radiation therapy.

Rachel's family history is significant for colon cancer. Her mother was diagnosed with colon cancer at age 66. Her paternal aunt was diagnosed with endometrial cancer at age 67. Rachel wonders if her endometrial cancer has a hereditary component.

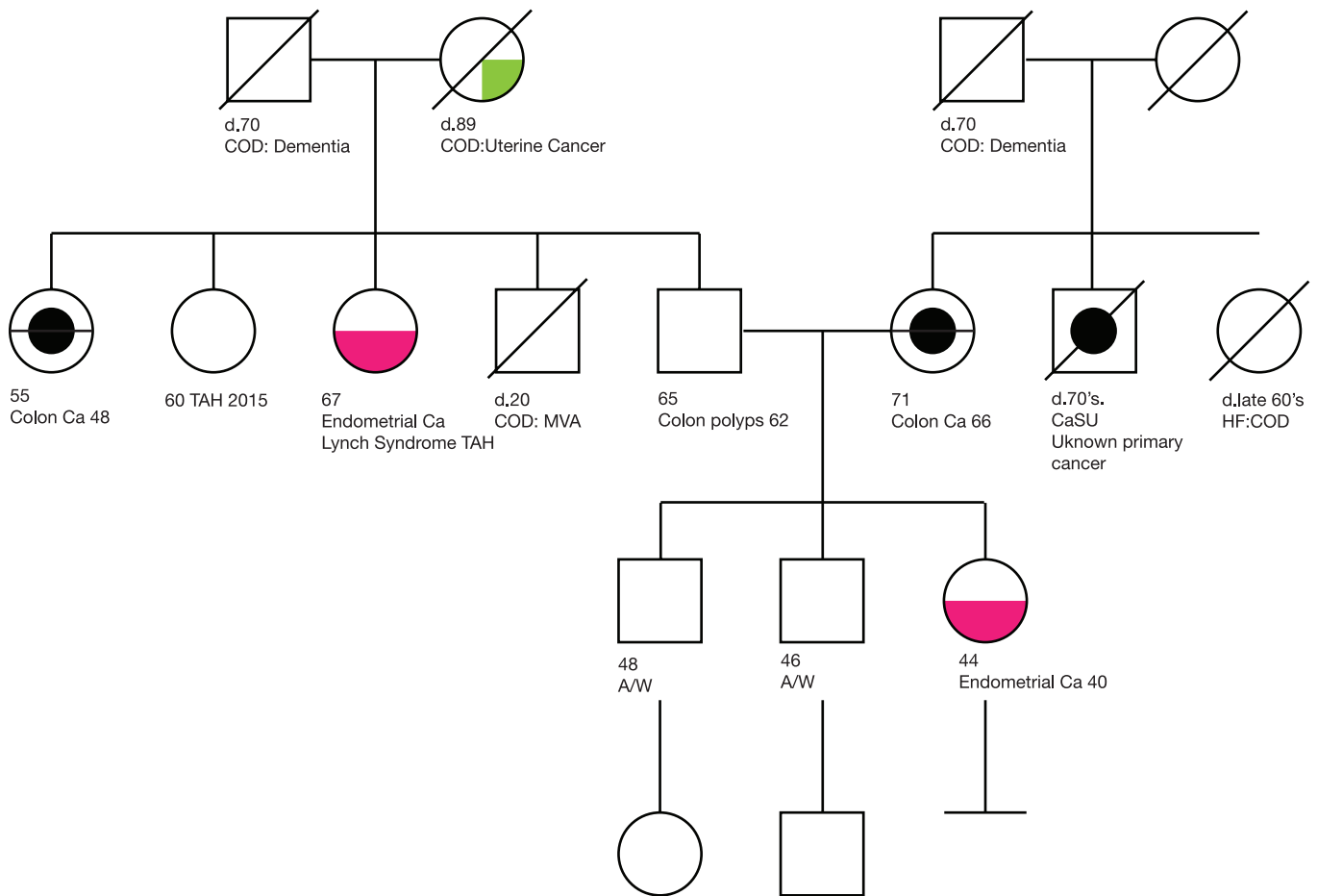


Fig. 1.

Pedigree of a family with Lynch syndrome. Members of the family have colorectal and endometrial cancer.

Questions

What is Lynch syndrome?

Lynch syndrome is the most common form of an inherited predisposition for colon cancer and endometrial cancer and is inherited in an autosomal dominant pattern. Lynch syndrome is also associated with an increased chance over a lifetime of developing cancers in other organs such as the stomach, ovary, and ureter/renal pelvis, among others. The increased risk for these cancers is due to inherited mutations that impair DNA mismatch repair. According to NCCN Lynch syndrome guidelines (v2.2015), surveillance for colon cancer should begin at 20-25 years of age and is repeated on a 1 to 2 year basis depending on the findings of the previous colonoscopy. Colon polyps associated with Lynch syndrome can progress to a malignancy in a 1 to 2 year period, compared to the often-quoted 10-year period for a sporadic colon polyp (NCCN v1.2015 Colon Cancer Screening).

The chances of developing cancer and the ages at which they might develop can vary depending on which DNA mismatch repair gene is affected. Cancer rates are much higher in *MLH1* and/or *MSH2* mutation carriers compared to *MSH6* and/or *PMS2* mutation carriers. The lifetime chance of developing endometrial cancer with an *MSH2* mutation is estimated to range from 25 to 60 percent (mean age of onset 48 to 62 years) versus a 15 percent lifetime chance in *PMS2* mutation carriers (mean age of onset at 49 years). In addition, the lifetime chance of developing ovarian cancer for *MSH2* mutation carriers is estimated to be between 4 and 24 percent (mean age of onset of 42 years) versus a 6 percent chance in *PMS2* mutation carriers (similar age of onset). Endometrioid ovarian cancer is the most common histologic type seen in Lynch syndrome.

A gynecologic malignancy may be the first presentation for a woman with Lynch syndrome; however, she is at risk for other malignancies, including a 40 to 80 percent lifetime risk of colon cancer. The gynecologic oncologist is an important provider to recognize the association and initiate surveillance to prevent a second primary tumor and further cancers in the family.

Who should be tested for Lynch syndrome?

Traditionally, testing for Lynch syndrome was recommended based on meeting relatively strict rules for personal and/or family history of colorectal and Lynch-related cancers (Bethesda or Amsterdam guidelines). However, these guidelines miss a large number of families that carry Lynch syndrome mutations. Since approximately 3 to 5 percent of all colorectal cancers are associated with Lynch syndrome, NCCN guidelines now recommend that all patients with colorectal cancer be screened for Lynch syndrome. A Centers for Disease Control and Prevention working group has endorsed that policy as cost-effective. Many experts are now recommending that universal screening of endometrial cancer patients be implemented since a similar risk (3-5%) of Lynch syndrome is found in patients with endometrial cancer.

When universal screening is not in place, SGO recommends that all patients with endometrial cancer undergo assessment of their personal and family history, with testing recommended for those with other Lynch syndrome-related tumors present.

How is testing done for Lynch syndrome?

Like women with personal or family histories suggestive of HBOC, those with personal and family histories suggestive for Lynch syndrome can be referred to genetic counseling and undergo genetic testing. However, women who are diagnosed with a Lynch related cancers such as endometrial, colorectal or ovarian cancer, can sometimes be identified by tumor testing. The tumor can be assessed with immunohistochemistry (IHC) for the presence or absence of DNA mismatch repair proteins, including *MLH1*, *MSH2*, *MSH6*, and *PMS2*. When expression of one or more of these proteins is absent, suspicion for Lynch syndrome increases. However, promoter methylation of *MLH1* must be considered when its expression is abnormal, as it is a common event in sporadic cancer. The tumor can also be assessed by microsatellite instability (MSI), which is usually quantified as high or low. Over 90 percent of Lynch syndrome tumors lack expression of one of the IHC proteins and/or are MSI-high. Algorithms vary between institutions as to whether IHC alone, MSI alone, or IHC and MSI in combination are used for Lynch syndrome screening. In patients such as Rachel who already meet Amsterdam criteria for Lynch syndrome based on personal and family history of cancer, they can be referred for genetic testing directly without first undergoing tumor testing.

When abnormal tumor test results are present, referral to a genetics professional is recommended for germline testing to confirm the presence of a Lynch syndrome mutation. Patients who are unaffected by cancer may undergo germline testing based on the suspected or known presence of a mutation in family members. In addition, Lynch syndrome genes are included in many multi-gene panels assessing hereditary cancer risk.

What surveillance is recommended for women with Lynch syndrome?

ACOG, NCCN, and SGO have the following recommendations:

- Colonoscopy every 1 to 2 years, beginning at age 20 to 25 years, or 2 to 5 years before the earliest cancer diagnosis in the family, whichever is earlier
- Keep menstrual calendar and report abnormal bleeding
- Endometrial biopsy every 1 to 2 years, beginning at age 30 to 35 years
- Hysterectomy with bilateral salpingo-oophorectomy by mid-40s

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General Resources

Alliance for Fertility Preservation

Working to increase information, resources and access to fertility preservation for cancer patients and the healthcare professionals who treat them

Breastcancer.org

Patient-oriented site addressing breast cancer and includes prophylactic surgery and management of menopause

FORCE Peer Navigation Program

A confidential, free service providing expert-reviewed resources and 1:1 personalized peer support by specially trained volunteers

FORCE KNOW MORE Campaign

Helping women diagnosed with ovarian cancer make informed medical decisions around their care, informing survivors that they meet national guidelines for genetic evaluation, and helping them uncover clues about their health

FORCE/National Society of Genetic Counselors: Genetic Information, Privacy and Discrimination

Foundation for Women's Cancer

As the official foundation of the Society of Gynecologic Oncology, FWC promotes patient education, awareness, and research in gynecologic oncology.

H.I.S. Breast Cancer Awareness

Informs, educates, brings awareness, and teaches prevention specific to breast cancer in men

Lynch Syndrome International

Serving our global communities by providing support for individuals afflicted with Lynch syndrome, creating public awareness, educating the general public and health care professionals, and providing support for Lynch syndrome research endeavors

National Cancer Institute (NCI)

The federal government's principal agency for cancer research and training

NCI Surveillance, Epidemiology, and End Results (SEER) Program

Working to provide information on cancer statistics in an effort to reduce the burden of cancer among the U.S. population

National Comprehensive Cancer Network

An alliance of 27 of the world's leading cancer centers devoted to patient care, research, and education, dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can live better lives

National Society of Genetic Counselors Find a Genetic Counselor

North American Menopause Society

Comprehensive site for both providers and patients with thorough discussion of menopause and treatment options

National Ovarian Cancer Coalition

Working to save lives by fighting tirelessly to prevent and cure ovarian cancer, and to improve the quality of life for survivors

Ovarian Cancer Research Fund Alliance

The largest global organization dedicated to advancing ovarian cancer research while supporting women and their families

Risk Assessment and Genetic Counseling for Hereditary Breast and Ovarian Cancer: Recommendations of the National Society of Genetic Counselors

U.S. Preventive Services Task Force

Working to improve the health of all Americans by making evidence-based recommendations about clinical preventive services such as screenings, counseling services, and preventive medications

Collaborating Organizations

American College of Obstetricians and Gynecologists

Dedicated to the advancement of women's health care and the professional and socioeconomic interests of its members through continuing medical education, practice, research, and advocacy

Bright Pink

On a mission to save women's lives from breast and ovarian cancer by empowering them to live proactively at a young age

FORCE: Facing Our Risk of Cancer Empowered

Working to improve the lives of individuals and families affected by hereditary breast, ovarian, and related cancers

National Society of Genetic Counselors

Advancing the various roles of genetic counselors in health care by fostering education, research, and public policy to ensure the availability of quality genetic services

Society of Gynecologic Oncology

Promoting the highest quality of comprehensive clinical care through education and research in the prevention and treatment of gynecologic cancers