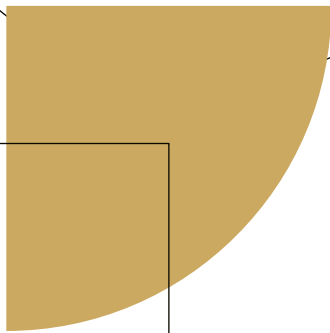
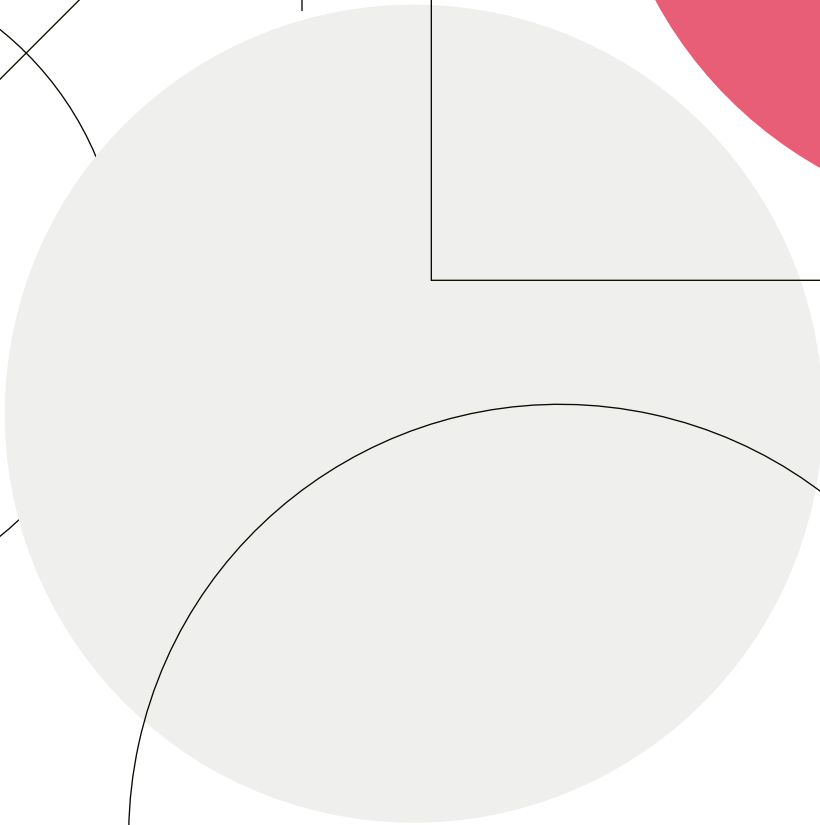




Society of Gynecologic Oncology



Society of **Gynecologic Oncology**

# 2020 GENETICS TOOLKIT

In collaboration with:



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



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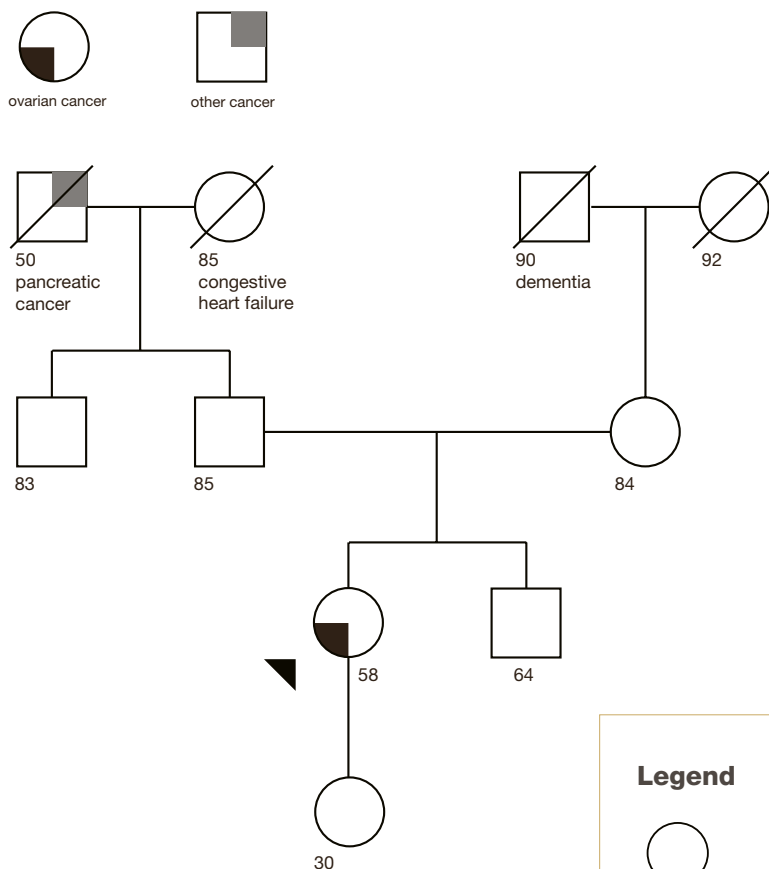
The purpose of this toolkit is to provide access to critical, practical information for health care providers, our patients, their families, and anyone interested in gaining a deeper understanding of the role of genetics in gynecologic cancers. As this is a collaborative effort of several societies, 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 comprises 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 mutation-related ovarian cancer

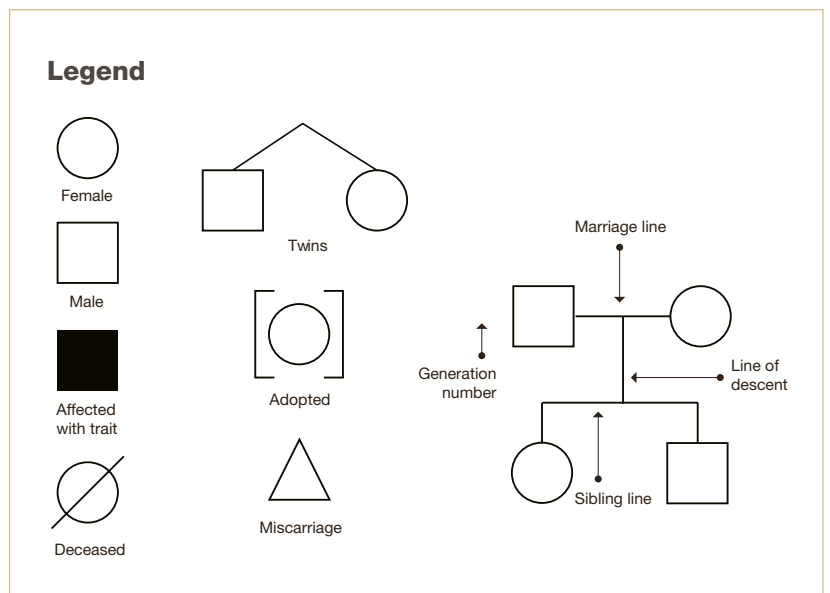
Janet is 58 years old and has a recent history of abdominal pain and bloating. Her primary care physician obtained a CT scan of her abdomen and pelvis. The scan showed a pelvic mass, thickening of the omentum (a fatty apron that hangs from the colon), and fluid accumulation (ascites). Janet was referred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



### Why is Janet's oncologist recommending genetic risk evaluation and testing for her?

About 20% of women with ovarian, fallopian tube, or primary peritoneal cancer 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. However, most experts feel these factors do not need to be present to recommend testing, 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 of referral for genetic risk evaluation and testing. Mucinous ovarian cancer represents a potential exception since it has not been shown to be part of hereditary breast and ovarian cancer (HBOC) syndrome and is rarely seen in Lynch syndrome. Genes that are part of HBOC syndrome increase the risk of breast cancer, ovarian cancer, and other cancers. The genes involved in Lynch syndrome increase the risk of colon, endometrial, ovarian, and other cancers.

### What types of genetic tests are available to Janet?

Traditionally, genetic testing has been performed for 1 to 2 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 the changes are in every cell and can be passed on to children. This process can be expensive and time-consuming if multiple genes are tested. More 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 with 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. According to the National Comprehensive Cancer Network (NCCN) 2019 guidelines, all women with epithelial ovarian, fallopian tube, and primary peritoneal cancer should be offered genetic risk evaluation and testing. The Society of Gynecologic Oncology (SGO) has endorsed that recommendation. NCCN guidelines include the statement that "when more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-

effective." Many experts would consider HBOC an example of an inherited syndrome where multiple genes can explain the disease pattern seen.

Clinical recommendations like enhanced cancer screening or risk-reducing surgery are reserved for those individuals who 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, 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 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 genetic testing shows a gene mutation. Survival from ovarian cancer is higher for women who have a *BRCA1* or *BRCA2* mutation compared with those who do not have a mutation, at least partially due to the fact that *BRCA1* and *BRCA2* mutation-related ovarian cancer may be more sensitive to platinum chemotherapy. If her ovarian cancer goes into remission, the presence of a *BRCA1* or *BRCA2* mutation might influence her decision to receive enhanced breast cancer screening. She might choose to take a PARP inhibitor as part of maintenance therapy or treatment if her ovarian cancer recurs. This new class of drugs called PARP inhibitors is particularly effective in women with *BRCA1* and *BRCA2* mutations. Currently, 3 PARP inhibitor drugs are FDA-approved in the United States for use in women with ovarian cancer in specific clinical situations. This is an active area of research with ongoing clinical trials and frequent updates to the indications for PARP inhibitors, so consultation with an oncologist who is an expert in their use is recommended for ovarian cancer patients.

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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. Janet was recently diagnosed with ovarian cancer at age 58 and has undergone genetic testing with a panel test including HBOC genes that documented 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; 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 run in the family, there is often significant relief of stress. 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 risk evaluation does not infer that genetic testing must be done. Some patients are not ready to move forward with testing immediately; genetic counseling gives them information to use at any place in their process of coming to terms with their hereditary risk.

#### What are Susan's options for obtaining genetic testing?

Many experts prefer a model where patients receive genetic counseling from a genetics professional before choosing to proceed with genetic testing. The relative scarcity of these genetics professional has led to alternative models with primary care providers or telehealth providers provide access to genetic testing with variable amounts of genetic counseling. Yet another option is direct-to-consumer (DTC) testing. Typically, the DTC entities are using models that are not validated for making clinical decisions and may have a substantial error rate in their interpretations. Results from DTC entities providing ancestry and health-based services need to be reviewed carefully with an experienced professional before being used to make clinical decisions. The U.S.

Preventive Services Task Force (USPSTF) recently updated its guidelines for women who have never been diagnosed with *BRCA* mutation-related cancer and those with *BRCA*-mutation related cancer who have completed treatment and are in remission. USPSTF recommends that specifically *BRCA1* and *BRCA2* mutation testing be offered to women with a personal and/or family history of breast, ovarian, fallopian tube, and/or primary peritoneal cancer who have a positive result on a risk assessment tool. They acknowledge the availability of multi-gene panel testing but feel their use requires further investigation. USPSTF did not review evidence about the benefit of genetic counseling and testing in men.

In this setting where Susan knows her mother carries a *BRCA1* mutation, Susan could be tested for the single site mutation carried by her mother. However, the potential for inherited cancer risk must always be assessed for both sides of a person's family to make sure the best test to address that risk is offered. If Susan's father's personal and family cancer history is concerning for a mutation in the paternal lineage, broader testing may be indicated. In addition, if Susan only knew about her mother's ovarian cancer diagnosis without specific knowledge of genetic testing, panel testing (such as her mother had) would be a reasonable option. NCCN guidelines include the statement that "when more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective". Many experts would consider HBOC an example of an inherited syndrome where multiple genes can explain the disease pattern seen.

#### Is genetic risk evaluation and testing typically covered by insurance? What is the typical cost of genetic testing?

Genetic risk evaluation and testing for individuals at risk for *BRCA* mutations are considered preventive services under the Affordable Care Act (ACA), 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, with the price of testing varying by company. Without insurance coverage, the cost of a full *BRCA1* and *BRCA2* analysis varies from about \$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, at similar cost to *BRCA1/2* testing. While comprehensive testing is required if a patient is the first in their family to undergo testing, a single site analysis (test that looks only for the family's known mutation) can be done for relatives of a patient who knows their specific mutation, frequently at a lower cost than comprehensive sequencing.

### **If a woman carries a *BRCA1* or *BRCA2* mutation, what surveillance and risk-reduction strategies are recommended for her?**

When a woman is found to carry a *BRCA1* or *BRCA2* mutation, heightened surveillance and risk-reduction options are available for her. Risk-reduction strategies are also available for some but not necessarily all of the genes that might be included in a panel test. For 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 the opportunity to reduce her risk of breast cancer by up to 97% through a risk-reducing mastectomy (surgical removal of breasts). 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 modulators (SERMs), which are associated with breast cancer risk reduction of up to 50%.

For ovarian cancer risk, using oral contraceptives, having a tubal ligation, or having a hysterectomy have been shown to decrease risk. However, surgical risk reduction with bilateral salpingo-oophorectomy (removal of the fallopian tubes and both ovaries), is recommended for all high-risk women after the conclusion of any desired childbearing as the most effective risk-reduction option. Because Susan is still interested in conceiving a child, she could consider twice yearly high-risk surveillance if she has a mutation. However, surveillance with pelvic exams, transvaginal ultrasound, and CA-125 blood test starting at the age of 30 has not been shown to prolong survival in mutation carriers.

When Susan has completed childbearing, she can consider risk-reducing surgery. 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 (removal of the ovaries) 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. In addition, many women are candidates for hormone replacement after BSO to minimize the side effects of menopause. Patients with a *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 salpingo-oophorectomy until 40-45 years of age. This strategy reduces the risk of ovarian and fallopian tube cancer, but does not confer additional risk reduction for breast cancer until the time of oophorectomy. In patients who choose mastectomy for breast cancer risk reduction, and who have not been previously diagnosed with breast cancer, estrogen replacement therapy is safe and reasonable. Hysterectomy (removal of the uterus) along with salpingo-oophorectomy is also an option based on personal factors discussed in Case 3.

### **Is fertility altered by a *BRCA1/2* 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 struggle to conceive even with 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.

Many *BRCA1/2* mutation carriers choose not to pursue PGD, at least partly because the mutations are associated primarily with risk of cancer in adulthood. One childhood condition that can occur in rare circumstances is Fanconi anemia, which happens when a person inherits a *BRCA2* mutation from each parent. For this reason, careful attention should be given to the family history of both 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 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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U.S. Preventive Services Task Force

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## Case 3: Risk-reducing salpingo-oophorectomy

Susan is now 40 years of age with a feisty 4 year-old and has decided to undergo a risk-reducing salpingo-oophorectomy (RRSO) because she carries a *BRCA1* mutation. 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?

RRSO is usually performed as a minimally invasive (laparoscopic) surgery that takes approximately 60 to 90 minutes. This outpatient surgery usually requires several small incisions. The abdomen is inspected thoroughly and a pelvic wash is collected for cytology to see if abnormal cells are present before the fallopian tubes and ovaries are manipulated. The blood supply to the ovary and tube is interrupted at 2 cm or more away from the ovary to ensure that all the ovarian tissue is removed. As much fallopian tube as possible is carefully removed from its junction with the uterus. An initial inspection by the pathologist is performed during the procedure to see if obvious cancer is present. After surgery, the ovaries and tubes are cut into 2-3 mm sections so that each section can be carefully examined by the pathologist for early cancer or pre-cancer. This special pathology procedure is critical to detect microscopic cancer and differs from the typical processing of tubes and ovaries for benign gynecologic surgery. The entire fallopian tube must be examined in careful detail as most of the pre-cancer and early cancer changes are found in the fallopian tube rather than the ovary.

#### What is the benefit of RRSO?

RRSO prevents approximately 80% 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% 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 are removed in their entirety and carefully examined for early cancers.

#### Should hysterectomy be performed along with RRSO?

Generally, the uterus and cervix are not at high risk for cancer in the same way the fallopian tubes and ovaries are in patients with *BRCA1* and *BRCA2* mutations, although data have suggested a small increased risk of serous endometrial cancer in *BRCA1* mutation carriers. Since serous uterine cancer is difficult to detect early, some women choose to have a hysterectomy at the time of RRSO in order to have maximum gynecologic cancer risk reduction. 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, which is associated with an increased uterine cancer risk. Still others may have 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 mucosal epithelium, that have not yet invaded to deeper tissues as a true invasive carcinoma would. They are almost always found on the fimbriae, the ends of the fallopian tubes 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. 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, experts 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 and hysterectomy have been associated with some risk reduction for 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

Susan (see Case 3) has undergone a laparoscopic RRSO for a *BRCA1* mutation at age 40. 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 oophorectomy can cause bothersome and persistent symptoms as well as a 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 overall 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 in their 60s. 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 receive realistic counseling about these outcomes and be prepared to address persistent symptoms. The references below provide resources available to women to improve menopausal symptoms.

#### 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% reduction in risk. Additionally, premenopausal oophorectomy is associated with a 50% 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% lifetime risk.

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, Janet's son and Susan's brother, 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) syndrome is the family member 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 mutation that causes HBOC in which first-degree relatives (parents, siblings, or children) of a mutation carrier are tested. This process is repeated for each subsequent mutation carrier identified. Cascade testing allows people at risk for cancer to be identified before they develop cancer, increasing the opportunity to be proactive about cancer risk.

#### 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 compared to the average man's cancer risk but not as high as the cancer risk for women with *BRCA1* and *BRCA2* mutations. This risk is higher for men with *BRCA2* mutations than *BRCA1* mutations. The cancers that can impact men include:

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

NCCN guidelines for risk management in men with mutations include:

- ◆ Starting at age 35 years:
  - ◆ Breast self-exam training and education
  - ◆ Clinical breast exam every 12 months
- ◆ Starting at age 45 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. In addition, male mutation carriers have a 50% chance of passing the mutation on to their children, whether they are boys or girls.

#### What are the reproductive concerns with *BRCA1* and *BRCA2* mutations?

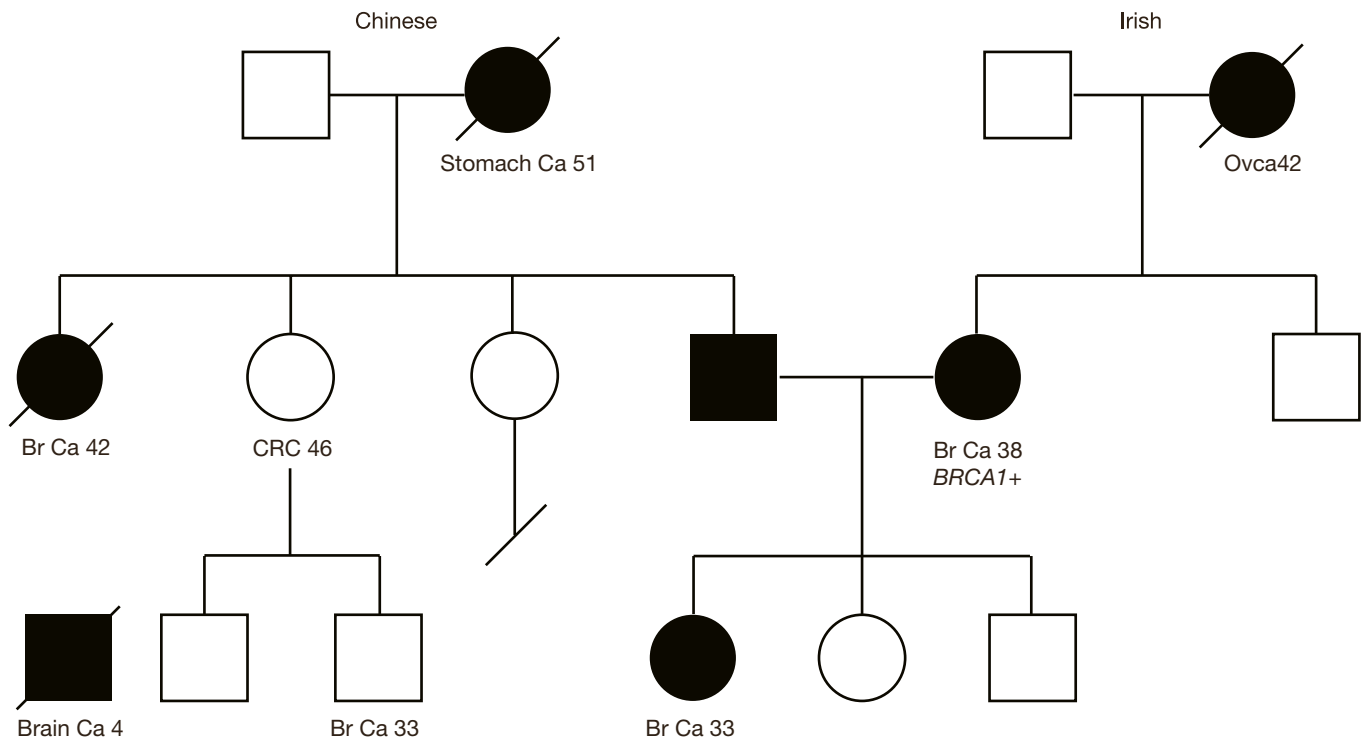
Preimplantation genetic diagnosis (PGD) can be used to select embryos for implantation that do not have a mutation. PGD would require that Rob's wife also undergo in vitro fertilization (IVF). These procedures can be costly and are often not covered by health insurance. Financial assistance programs 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. *BRCA1* and *BRCA2* mutations are associated with cancer risk as an adult, with significant potential for screening and risk reduction, except in the rare circumstance that both parents are *BRCA* mutation carriers.

In families where one parent who carries a mutation in one of the *BRCA*/Fanconi anemia pathway genes, their partner may be offered testing for the same gene because children who inherit mutations in the same gene from both parents are at risk for Fanconi anemia, an inherited form of aplastic anemia. This disease usually appears at birth or early childhood and can be associated with at least 15 genes in the Fanconi anemia pathway, including *BRIP1*, *BRCA2*, and *RAD51C*.



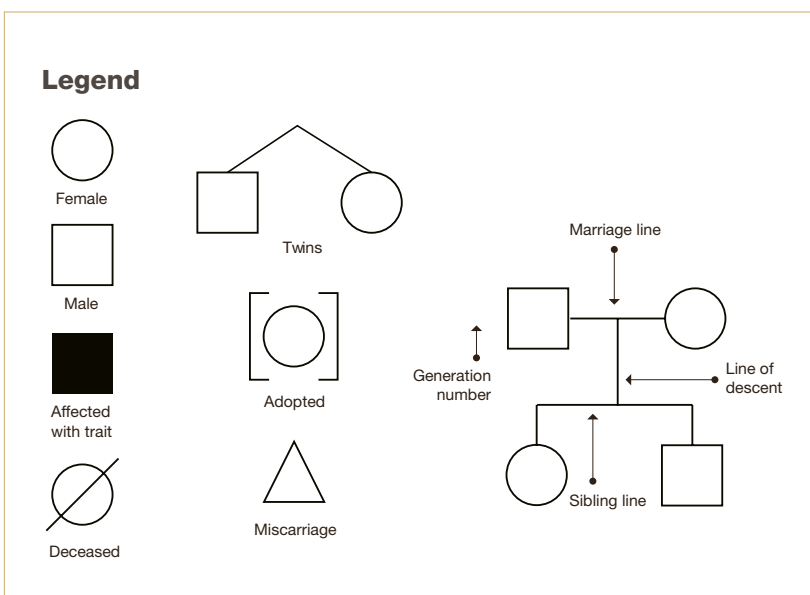
## Case 6: Ambiguous test results and variants

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.



### Should Mary consider further genetic testing?

Yes, 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 (NCCN) guidelines recommend consideration of genetic testing for women diagnosed with breast cancer  $\leq 45$  years old. A second reason is her strong paternal family history of cancer. Most inherited cancer risks 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. Genes and their variants can have variable penetrance, meaning that a low, moderate or high proportion of people can be affected by the trait associated with the gene or variant, which in this

context is increased risk for cancer. While most cancer susceptibility genes are rare and highly penetrant, our understanding of genes with low and moderate penetrance is increasing, with *ATM*, *BARD1*, *BRIP1*, and *CHEK2* as examples in HBOC. 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 risk evaluation 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.

### Since Mary was found to carry a variant of uncertain significance (VUS), what does this mean to her 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 or likely pathogenic) 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 unless the commercial lab offers for the family to participate in a variant study.

### 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 breast cancer sporadically at a young age.

### **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 history may not be explained by the *BRCA1* mutation on the maternal side. Management recommendations 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 risk evaluation to consider appropriate genetic testing based on his diagnosis of cancer and family history of cancer. 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 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.

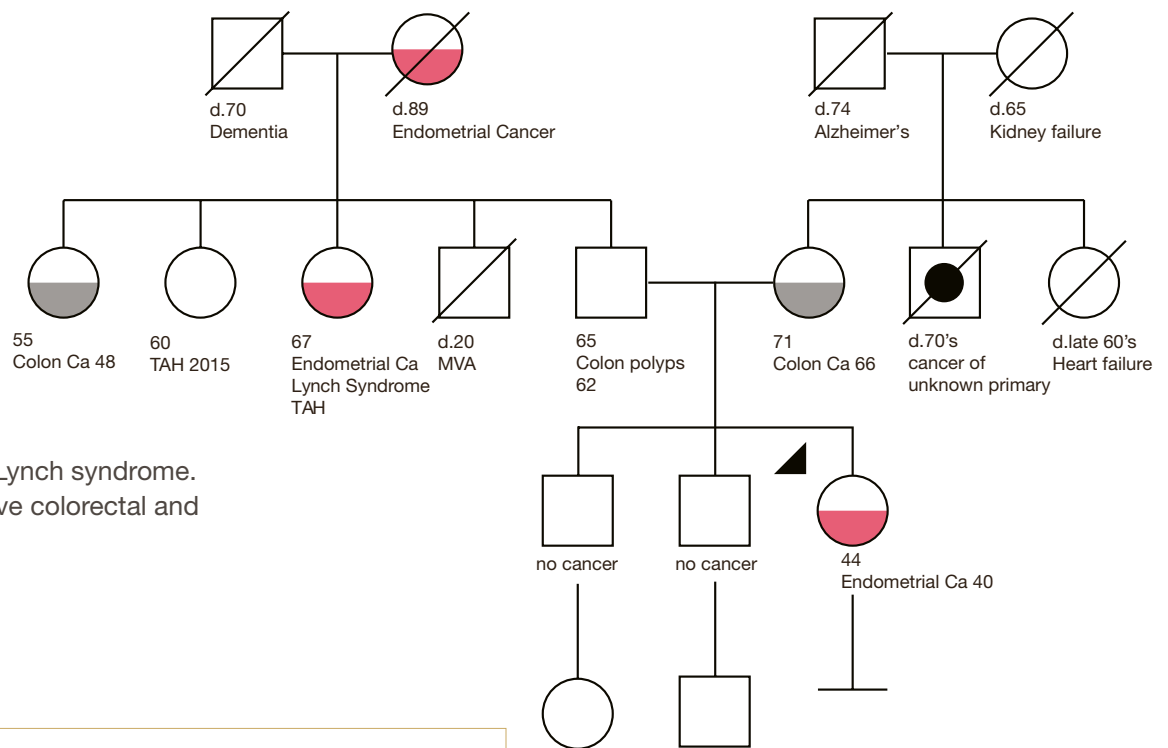
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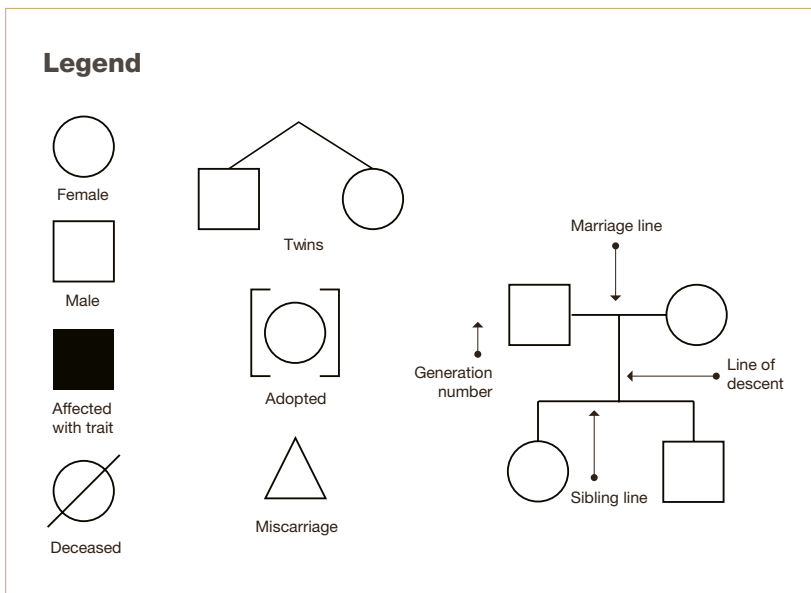
## Case 7: Lynch syndrome

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 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.



### What is Lynch syndrome?

Lynch syndrome is the most common form of an inherited predisposition for colon and endometrial cancer and is inherited in an autosomal dominant pattern, meaning that a parent of either sex with a mutation has a 50% chance of passing it on to a child of either sex. Lynch syndrome is also associated with an increased chance of developing cancers in other organs such as the stomach, ovary, and ureter/renal pelvis over a lifetime. The increased risk for these cancers is due to inherited mutations that impair DNA mismatch repair. According to NCCN guidelines, surveillance for colon cancer should begin at 20-25 years of age (or 2-5 years prior to the earliest colon cancer in the family if it was diagnosed before age 25) 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.

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 *MLH1* or *MSH2* mutation is estimated to range from 25 to 60% (mean age of onset 48 to 62 years) versus a 15% lifetime chance in *PMS2* mutation carriers (mean age of onset at 49 years). In addition, the chance of developing ovarian cancer for *MLH1* and *MSH2* mutation carriers by age 70 is estimated to be 11 to 24% (mean age of onset of 43 to 45 years) versus a much lower risk for *MSH6* and *PMS2* mutation carriers based on limited data. Endometrioid ovarian cancer is the most common histologic type seen in Lynch syndrome. Because of the variable risk of cancer associated with each specific Lynch mutation, it is important to individualize recommendations based on age and mutation.

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 60% 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% of all colorectal cancers are associated with Lynch syndrome, NCCN guidelines now recommend that all patients with colorectal and endometrial cancer be screened for Lynch syndrome. A Centers for Disease Control and Prevention working group has endorsed that policy as cost-effective.

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 syndrome, those with personal and family histories suggestive of Lynch syndrome can be referred for genetic risk evaluation and undergo germline genetic testing. However, women who are diagnosed with a Lynch syndrome-related cancer such as endometrial or colorectal cancer, can have tumor screening as a first step. 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 endometrial cancer. The tumor can also be assessed for microsatellite instability (MSI), which is usually quantified as high or low. Over 90% 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 germline genetic testing directly without first undergoing tumor testing. One consideration in this circumstance is that if germline testing were negative for a mutation, knowledge of tumor MSI and/or IHC status might make the patient eligible for immunotherapy if the tumor is documented to have mismatch repair deficiency.

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.

Consideration also may be given to risk-reducing strategies such as the use of hormonal contraception, which has been shown to decrease endometrial, ovarian, and colon cancer risk substantially, especially with 5 years or more of use.

### **What surveillance is recommended for women with Lynch syndrome?**

ACOG, NCCN, and SGO have the following recommendations for women with Lynch syndrome:

- ◆ 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 for prompt evaluation
- ◆ Endometrial biopsy every 1 to 2 years can be considered starting at age 30-35.
- ◆ Transvaginal ultrasound can be considered after menopause.
- ◆ Hysterectomy with bilateral salpingo-oophorectomy can be considered based on desire for childbearing, comorbidities, family history, and specific LS gene involved.

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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 health care 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 Alliance**

The leading organization in the world fighting ovarian cancer from all fronts, including in the lab and on Capitol Hill, 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