## **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 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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