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.

References

J. Balmaña, O. Díez, I.T. Rubio, F. Cardoso; ESMO Guidelines Working Group. BRCA in breast cancer: ESMO Clinical Practice Guidelines. Ann. Oncol. 22 (Suppl. 6) (2011) vi31-34.

J.L. Berliner, A.M. Fay, S.A. Cummings, B. Burnett, T. Tillmanns. NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. J. Genet. Couns. 22 (2) (2013) 155-163.

S.M. Domchek, T.M. Friebel, C.F. Singer, D.G. Evans, H.T. Lynch, C. Isaacs, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 304 (9) (2010) 967-975.

A. Finch, K.A. Metcalfe, J. Chiang, L. Elit, J. McLaughlin, C. Springate, et al. The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation. Psycho-Oncology 22 (1) (2013) 212-219.

A. Finch, A. Valentini, E. Greenblatt, H.T. Lynch, P. Ghadirian, S. Armel, S.L. Neuhausen, C. Kim-Sing, N Tung, B.Y. Karlan, W.D. Foulkes, P. Sun, S. Narod; Hereditary Breast Cancer Study Group. Frequency of premature menopause in women who carry a BRCA1 or BRCA2 mutation. Fertil Steril. 99 (6) (2013) 1724-8

B. Fisher, J.P. Costantino, D.L. Wickerham, R.S. Cecchini, W.M. Cronin, A. Robidoux, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J. Natl. Cancer Inst. 97 (22) (2005) 1652-1662.

J.M. Lancaster, C.B. Powell, N.D. Kauff, I. Cass, L.M. Chen, K.H. Lu, et al; Society of Gynecologic Oncologists Education Committee. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol. Oncol. 107 (2) (2007) 159-162.

E.M. Mikkelsen, L. Sunde, C. Johansen, S.P. Johnsen. Psychosocial consequences of genetic counseling: a population-based follow-up study. Breast J. 15 (1) (2009) 61-8.

H.D. Nelson, M. Pappas, B. Zakher, J.P. Mitchell, L. Okinaka-Hu, R. Fu. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann. Intern. Med. 160 (4) (2014) 255-266.

H.D. Nelson, L.H. Huffman, R. Fu, E.L. Harris; U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. Ann. Intern. Med. 143 (5) (2005) 362-379.

H.D. Nelson, M.E. Smith, J.C. Griffin, R. Fu. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann. Intern. Med. 158 (8) (2013) 604-614.

A.H. Pieterse, M.G. Ausems, P. Spreeuwenberg, S. van Dulmen. Longer-term influence of breast cancer genetic counseling on cognitions and distress: smaller benefits for affected versus unaffected women. Patient Educ. Couns. 85 (3) (2011) 425-431.

M.E. Robson, C.D. Storm, J. Weitzel, D.S. Wollins, K. Offit; American Society of Clinical Oncology. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J. Clin. Oncol. 28 (5) (2010) 893-901.

A.B. Skytte, D. Crüger, M. Gerster, A.V. Laenkholm, C. Lang, K. Brøndum-Nielsen, et al. Breast cancer after bilateral risk-reducing mastectomy. Clin. Genet. 79 (5) (2011) 431-437.

V.G. Vogel, J.P. Costantino, D.L. Wickerham, W.M. Cronin, R.S. Cecchini, J.N. Atkins, et al; National Surgical Adjuvant Breast and Bowel Project. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 trial: preventing breast cancer. Cancer Prev. Res. 3 (6) (2010) 696-706.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 103: hereditary breast and ovarian cancer syndrome. Obstet. Gynecol. 113 (4) (2009) 957-966.

E.T. Wang, M.D. Pisarska, C. Bresee, Y.I. Chen, J. Lester, Y. Afshar, C. Alexander, B.Y. Karlan. BRCA1 germline mutations may be associated with reduced ovarian reserve. Fertil. Steril. 102 (6) (2014) 1723-1728. doi: 10.1016/j.fertnstert.2014.08.014. Epub 2014 Sep 23.

K. Otkay, J.Y. Kim, D. Barad, S.N. Babayev. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks. J. Clin. Oncol. 28 (2) (2010) 240–244. Published online 2009 Dec 7. doi: 10.1200/JCO.2009.24.2057 PMCID: PMC3040011.

M. Sagi, N. Weinberg, A. Eilat, E. Aizenman, M. Werner, E. Girsh, et al. Preimplantation genetic diagnosis for BRCA1/2--a novel clinical experience. Prenat. Diagn. 29 (5) (2009) 508-513. doi: 10.1002/pd.2232.

M. Drüsedau, J.C. Dreesen, I. Derks-Smeets, E. Coonen, R. van Golde, J. van Echten-Arends, et al. PGD for hereditary breast and ovarian cancer: the route to universal tests for BRCA1 and BRCA2 mutation carriers. Eur. J. Hum. Genet. 21 (12) (2013) 1361-1368. doi: 10.1038/ejhg.2013.50. Epub 2013 Mar 27.