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*.