



ObGyns counsel many women with a personal or family history of breast cancer. Many of these patients can benefit from genetics counseling and testing. This particular patient has a family history of breast cancer and metastatic prostate cancer on her maternal side, which raises a “red flag” for hereditary cancer syndrome.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

Who needs breast cancer genetics testing?

Identifying patients who are appropriate candidates for breast cancer genetics testing is a key step toward prevention and value-based care

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Advances in cancer genetics are rapidly changing how clinicians assess an individual's risk for breast cancer. ObGyns counsel many women with a personal or family history of the disease, many of whom can benefit from genetics counseling and testing. As patients with a hereditary predisposition to breast cancer are at higher risk and are younger at diagnosis, it is imperative to identify them early so they can benefit from enhanced surveillance, chemoprevention, and discussions regarding risk-reducing surgeries. ObGyns are uniquely poised to identify young women at risk for hereditary cancer syndromes, and they play a crucial role in screening and prevention over the life span.

CASE Patient with breast cancer history asks about screening for her daughters

A 52-year-old woman presents for her annual examination. She underwent breast cancer treatment 10 years earlier and has done well since then. When asked about family history of breast cancer and ethnicity, she reports her mother had breast cancer later in life, and her mother's father was of Ashkenazi Jewish ancestry. In addition, a maternal uncle had metastatic



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Take-home points

- The best genetics test is a good family history, updated annually
- Each year, 35,000 breast cancers are attributable to hereditary risk
- It is crucial to identify families at risk for hereditary breast cancer early, as cancers may begin in a woman's 30s; screening begins at age 25
- Multigene panel testing is efficient and cost-effective
- For patients who have highly penetrant pathogenic variants and are of childbearing age, preimplantation genetics diagnosis is an option

prostate cancer. You recall that breast cancer diagnosed before age 50 years and Ashkenazi ancestry are "red flags" for a hereditary cancer syndrome. The patient wonders how her daughters should be screened. What do you do next?

Having a risk assessment plan is crucial

Given increasing demands, limited time, and the abundance of information to be discussed with patients, primary care physicians may find it challenging to assess breast cancer risk, consider genetics testing for appropriate individuals, and counsel patients about risk management options. The process has become even more complex since the expansion in genetics knowledge and the advent

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TABLE Rule of 1–2–3 for hereditary breast and ovarian cancer

Who needs breast cancer genetics testing?
<p>1 diagnosis in patient or first- or second-degree relative^a</p> <ul style="list-style-type: none"> Breast cancer at age <50 years Ovarian cancer at any age Triple-negative breast cancer at age ≤60 years Male breast cancer at any age Metastatic prostate cancer at any age Ashkenazi descent with breast, ovarian, pancreatic, or 2 aggressive prostate cancers at any age Known mutation carrier for breast cancer susceptibility gene
<p>2 diagnoses in patient or family member(s)^a</p> <ul style="list-style-type: none"> 2 primary breast cancers in 1 person, with first diagnosis made at age <50 years 2 relatives diagnosed with breast cancer, with 1 at age <50 years
<p>3 diagnoses (breast, ovarian, pancreatic, or aggressive prostate cancer, in any combination) on same side of family at any age^b</p>

Adapted from National Comprehensive Cancer Network,¹² American College of Obstetricians and Gynecologists,¹⁵ US Preventive Services Task Force,³¹ and American Society of Breast Surgeons³² publications.

^aFirst-degree relatives include parents, siblings and children; second-degree relatives include half-siblings, grandparents, aunts, uncles, nieces, nephews, and grandchildren.

^bIn this category only, third-degree relatives (eg, first cousins, great-grandparents, great-aunts, great-uncles, great-grandchildren) may be considered.

of multigene panel testing. Not only is risk assessment crucial for this woman and her daughters, and for other patients, but a delay in diagnosing and treating breast cancer in patients with hereditary and familial cancer risks may represent a worrisome new trend in medical litigation.^{1,2} Clinicians must have a process in place for assessing risk in all patients and treating them appropriately.

The American Cancer Society (ACS) estimated that 252,710 cases of breast cancer would be diagnosed in 2017, leading to 40,610 deaths.³ Twelve percent to 14% of breast cancers are thought to be related to hereditary cancer predisposition syndromes.⁴⁻⁸ This means that, every year, almost 35,000 cases of breast cancer are attributable to hereditary risk. These cases can be detected early with enhanced surveillance, which carries the highest chance for cure, or prevented with risk-reducing surgery in identified genetic mutation carriers. Each child of a person with a genetic mutation predisposing to breast cancer has a 50% chance of

inheriting the mutation and having a very high risk of cancer.

In this patient’s case, basic information is collected about her cancer-related personal and family history.

Asking a few key questions can help in stratifying risk:

- Have you or anyone in your family had cancer? What type, and at what age?
- If breast cancer, did it involve both breasts, or was it triple-negative?
- Is there a family history of ovarian cancer?
- Is there a family history of male breast cancer?
- Is there a family history of metastatic prostate cancer?
- Are you of Ashkenazi Jewish ethnicity?
- Have you or anyone in your family ever had genetics testing for cancer?

The hallmarks of hereditary cancer are multiple cancers in an individual or family; young age at diagnosis; and ovarian, pancreatic, or another rare cancer. Metastatic prostate cancer was added as a red flag for hereditary risk after a recent large series found that 11.8% of men with metastatic prostate cancer harbor germline mutations.⁹

CASE Continued

On further questioning, the patient reports she had triple-negative (estrogen receptor–, progesterone receptor–, and human epidermal growth factor receptor 2 [HER2]–negative) breast cancer, a feature of patients with germline *BRCA1* (breast cancer susceptibility gene 1) mutations.¹⁰ In addition, her Ashkenazi ancestry is concerning, as there is a 1-in-40 chance of carrying 1 of the 3 Ashkenazi founder *BRCA* mutations.¹¹ Is a genetics consultation needed?

Guidelines for genetics referral and testing

According to the **TABLE**, which summarizes national guidelines for genetics referral, maternal and paternal family histories are equally important. Our patient was under age 50 at diagnosis, has a history of triple-negative breast cancer, is of Ashkenazi ancestry, and has a family history of metastatic prostate cancer. She meets the criteria

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for genetics testing, and screening for her daughters most certainly will depend on the findings of that testing. If she carries a *BRCA1* mutation, as might be anticipated, each daughter would have a 50% chance of having inherited the mutation. If they carry the mutation as well, they would begin breast magnetic resonance imaging (MRI) screening at age 25.¹² If they decide against genetics testing, they could still undergo MRI screening as untested first-degree relatives of a *BRCA* carrier, per ACS recommendations.¹³

Integrating evidence and experience

Over the past 10 to 20 years, other breast cancer susceptibility genes (eg, *BRCA2*, *PALB2*, *CHEK2*) have been identified. More recently, next-generation sequencing has become commercially available. Laboratories can use this newer method to sequence multiple genes rapidly and in parallel, and its cost is similar to that of single-syndrome testing.¹⁴ When more than 1 gene can explain an inherited cancer syndrome, multigene panel testing may be more efficient and cost-effective. Use of multigene panel testing is supported in guidelines issued by the National Comprehensive Cancer Network,¹² the American College of Obstetricians and Gynecologists,¹⁵ and other medical societies.

For our patient, the most logical strategy would be to test for the 3 mutations most common in the Ashkenazi population and then, if no mutation is found, perform multigene panel testing.

Formal genetics counseling can be very helpful for a patient, particularly in the era of multigene panel testing.^{16,17} A detailed pedigree (family tree) is elicited, and a genetics specialist determines whether testing is indicated and which test is best for the patient. Possible test findings are explained. The patient may be found to have a pathogenic variant with associated increased cancer risk, a negative test result (informative or uninformative), or a variant of uncertain significance (VUS). VUS is a gene mutation identified with an unknown effect on protein function and an unclear association with cancer risk. A finding of VUS may make the patient anxious,¹⁸

create uncertainty in the treating physician,¹⁹ and lead to harmful overtreatment, excessive surveillance, or unnecessary use of a preventive measure.¹⁹⁻²¹ Genetics counseling allows the patient, even the patient with VUS, to make appropriate decisions.²² Counseling may also help a patient or family process emotional responses, such as fear and guilt. In addition, counselors are familiar with relevant laws and regulations, such as the Genetic Information Nondiscrimination Act of 2008 (GINA), which protects patients from insurance and employment discrimination. Many professional guidelines recommend providing genetics counseling in conjunction with genetics testing,^{12,23} and some insurance companies and some states require counseling for coverage of testing.

Cost of genetics counseling. If patients are concerned about the cost of genetics testing, they can be reassured with the following information²⁴⁻²⁶:

- The Patient Protection and Affordable Care Act (ACA) identifies *BRCA* testing as a preventive service
- Medicare provides coverage for affected patients with a qualifying personal history
- 97% of commercial insurers and most state Medicaid programs provide coverage for hereditary cancer testing
- Most commercial laboratories have affordability programs that may provide additional support.

If a *BRCA* mutation is found: Many patients question the value of knowing whether they have a *BRCA* mutation. What our patient, her daughters, and others may not realize is that, if a *BRCA* mutation is found, breast MRI screening can begin at age 25. Although contrast-enhanced MRI screening is highly sensitive in detecting breast cancer,²⁷⁻²⁹ it lacks specificity and commonly yields false positives.

Some patients also worry about overdiagnosis with this highly sensitive test. Many do not realize that preventively prescribed oral contraceptives can reduce the risk of ovarian cancer by 50%, and cosmetically acceptable risk-reducing breast surgeries can reduce the risk by 90%.

FAST TRACK

*Suggest genetics counseling when patients are concerned about the cost of genetics testing, question the value of knowing they have a *BRCA* mutation, or worry about overdiagnosis*

Many are unaware of the associated risks with ovarian, prostate, pancreatic, and other cancers; of risk management options; and of assisted reproduction options, such as pre-implantation genetics diagnosis, which can prevent the passing of a genetic mutation to future generations. The guidelines on risk management options are increasingly clear and helpful,^{12,30-32} and women often turn to their ObGyns for advice about health and prevention.

ObGyns are often the first-line providers for women with a personal or family history of breast cancer. Identification of at-risk patients begins with taking a careful family history and becoming familiar with the rapidly evolving

guidelines in this important field. Identification of appropriate candidates for breast cancer genetics testing is a key step toward prevention, value-based care, and avoidance of legal liability.

CASE Resolved

In this case, testing for the 3 common Ashkenazi *BRCA* founder mutations was negative, and multigene panel testing was also negative. Her husband is not of Ashkenazi Jewish descent and there is no significant family history of cancer on his side. The daughters are advised to begin high-risk screening at the age of 32, 10 years earlier than their mother was diagnosed, but no genetic testing is indicated for them. ●

FAST TRACK

Identifying those who are appropriate for breast cancer genetics testing is a key step toward prevention, value-based care, and avoidance of legal liability

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