

Managing a woman with *BRCA* mutations? Shared decision-making is key

A collaborative assessment of options and trade-offs—perhaps using visual decision aids—can help.

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PRACTICE RECOMMENDATIONS

➤ *Recommend genetic screening for the BRCA mutation if a patient's family history includes a breast cancer diagnosis before age 50, occurrences of both breast and ovarian cancers, or other suggestive features.* (C)

➤ *Advise women with the BRCA gene to return for a clinical breast exam every 6 to 12 months starting at age 25, and to start radiologic screening at age 30.* (C)

➤ *Consider recommending bilateral salpingo-oophorectomy to prevent ovarian cancer in women 35 to 40 years of age with a BRCA1 mutation who have completed childbearing.* (C)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶

Sara T* recently moved back to the area to be closer to her family. The 34-year-old patient visited our office to discuss the benefits and potential risks of genetic counseling. She explained that her aunt had just died at age 64 of ovarian cancer. Also, her maternal cousin had been diagnosed at age 42 with breast cancer, and her maternal grandmother had died at age 45 of an unknown “female cancer.” She was scared to find out if she had high-risk genes because she felt it would change her life forever. However, if she ignored the issue, she thought she might worry too much.

We discussed the implications of a positive result, such as having to live with the knowledge and to make decisions about potential screening and risk-reducing surgery. On the other hand, not knowing could allow for the undetected growth of cancer that might otherwise be mitigated to some degree if she knew her risk status and pursued an aggressive screening program.

We worked with Ms. T to map out her next steps.

**The patient's name has been changed to protect her identity.*

Breast cancer is the most commonly diagnosed cancer in women worldwide, representing nearly one-quarter of all female cancer diagnoses in 2018.¹ It is the second-leading cause of cancer death in women in developed nations and the leading cause of cancer death in women in developing nations.¹ In the United States, 1 in 8 women will develop breast cancer in her lifetime.² By comparison, the rate of ovarian cancer is much lower, with a lifetime prevalence of 1 in 70 to 80 women.^{3,4} Although ovarian cancer is less common than breast cancer, its associated mortality is high, and most cases are discovered at advanced stages.

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➤ USPSTF now also recommends *BRCA1/2* screening for any woman with a family history of tubal or peritoneal cancer.

■ **The outsized threat of *BRCA* mutations.** It is estimated that 5% to 10% of all breast cancers are hereditary, with 80% of these attributable to *BRCA1* (45%) and *BRCA2* (35%).⁵ These autosomal dominant mutations occur at the germline level, within the egg or sperm, and are therefore incorporated into the DNA of every cell and passed from one generation to the next. Families with *BRCA* mutations have much higher lifetime rates of cancer. The lifetime risk of breast cancer due to *BRCA* mutations is estimated at > 80% (*BRCA1*) and 45% (*BRCA2*).⁵ *BRCA* mutations account for between 10% and 18% of all ovarian cancers⁶ and convey a lifetime risk of 40% (*BRCA1*) and 15% (*BRCA2*) to carriers.⁵

Male *BRCA* carriers have a lifetime breast cancer risk of 1% to 5% with *BRCA1* and 5% to 10% with *BRCA2*,^{7,8} compared with about 1:1000 lifetime incidence in the unselected male population. Male carriers are also at risk for more aggressive prostate cancers.^{7,8}

■ **Certain populations carry undue burden of *BRCA*-related disease** due to specific founder mutations. While the estimated global prevalence of *BRCA* mutations is 0.2% to 1%, for those of Ashkenazi Jewish descent the range is 2% to 3%, representing a relative risk up to 15 times that of the general population.⁹ Hispanic Americans also appear to have higher rates of *BRCA*-related cancers.¹⁰ Ongoing genetics research continues to identify founder mutations worldwide,¹⁰ which may inform future screening guidelines.

In addition to *BRCA* mutations, there are other, less common mutations (TABLE 1⁵) known to cause hereditary breast and ovarian cancer.

■ **Identifying *BRCA* genes enables treatment planning.** Compared with sporadic cancers, *BRCA*-related breast cancers are diagnosed at earlier ages,¹¹ are more likely to have lymph node involvement at time of discovery,¹² are more likely to be triple negative (no expression of estrogen, progesterone, or *HER2* receptors),^{11,12} and are associated with worse overall and breast cancer-specific survival.¹³

Similarly, *BRCA*-related ovarian cancer is more likely to be high-grade and endometrioid or serous subtype.¹⁴ Knowledge of *BRCA* carrier status allows for risk-reducing strategies

that are effective in reducing the incidence of cancer and improving cancer-specific survival.^{15,16} As such, it is crucial that the primary care provider understand guidelines to help identify this high-risk population and work with patients on risk-reducing strategies.

Shared decision-making helps give clarity to the way forward

Shared decision-making is a process of communication whereby the clinician and the patient identify a decision to be made, review data relevant to clinical options, discuss patient perspectives and preferences regarding each option, and arrive at the decision together.¹⁷ Shared decision-making is important when treating women with *BRCA* mutations because there is no single correct plan. Individual values and competing medical issues may strongly guide each woman's decisions about screening and cancer prevention treatment decisions.

Shared decision-making in this situation is a strategy to use the evidence of risk along with patient preferences around fertility issues to help come to a decision that is the right one for the patient. Primary care clinicians aware of the general risks and benefits of each available option can refer women at high risk for breast or ovarian cancer to a specialist multidisciplinary clinic that can provide tailored risk assessment and risk reduction counseling as needed.¹⁸⁻²⁰

Genetic screening recommendations

Screening is recommended for women who have any 1 of several family risk factors (TABLE 2²¹). A number of risk assessment tools are available for primary care clinicians to determine which patients are at high enough risk for a hereditary breast or ovarian cancer to warrant referral to a genetic counselor.²²⁻²⁵ If screening suggests high risk, the US Preventive Services Task Force (USPSTF) recommends (Grade **B**) referral for genetic counseling.²¹

Explain to patients who are candidates for further investigation that a genetic counselor will review their family history and recommend testing for the specific mutations that increase cancer risk. Discuss po-

TABLE 1

Genes associated with breast cancer⁵

Each mutation other than *BRCA1/2* accounts for < 1% of hereditary breast and ovarian cancers.

<i>ATM</i> (ataxia-telangiectasia)	<i>MAP3K1</i>
<i>BARD1</i>	<i>MRE11</i>
<i>BRCA1/2</i>	<i>MSH2/MLH1</i> (Muir-Torre syndrome)
<i>BRIP1</i>	<i>NBN</i>
<i>CASP8</i>	<i>p53</i> (Li-Fraumeni syndrome)
<i>CDH1</i>	<i>PALB2</i>
<i>CHEK2</i>	<i>PTEN</i> (Cowden disease)
<i>CTLA4</i>	<i>RAD51</i>
<i>CYP19A1</i>	<i>STK11/LKB1</i> (Peutz-Jeghers syndrome)
<i>FGFR2</i>	<i>TERT</i>
<i>H19</i>	<i>TOX3</i>
<i>LSP1</i>	<i>XRCC2, XRCC3</i>

tential benefits and harms of genetic testing. A benefit of genetic testing is that aggressive screening may suggest preventive procedures to reduce the risk of future cancer. Most tests come back definitively positive or negative, but an indeterminate result may cause harm. A small minority of results may indicate a genetic variant of unknown significance. The ramifications of this variant may not be known. Some women will experience anxiety about nonspecific test results and will be afraid to share them with family members. There is also some concern about privacy issues, potential insurance bias, and coverage of any preventive strategies.²⁶

CASE ►

Based on Ms. T's family history and her desire to know more, we referred her to a genetic counselor and she decided to undergo genetic testing. She screened positive for *BRCA1*. Ms. T was in a serious relationship and thought she would like to have children at some point. She returned to our office after receiving the positive genetic test results, wondering about screening for breast and ovarian cancer.

Breast cancer screening and risk-reduction strategies

■ **Screening.** Because the risk of breast cancer is high in women with *BRCA* mutations,

and because cancer in these women is more likely to be advanced at diagnosis, starting a screening program at an early age is prudent. Observational studies suggest that breastfeeding reduces the risk of breast and ovarian cancer in women with *BRCA* mutations, as it does for women in the general population.²⁷ Women should return for a clinical breast exam every 6 to 12 months starting at age 25; they should start radiologic screening with magnetic resonance imaging at age 25 and mammography at age 30 (TABLE 3^{27,28}).

■ **Risk-reduction strategies.** There is weak evidence to support the use of tamoxifen or other synthetic estrogen reuptake modulators (SERMs) to reduce breast cancer risk in women with *BRCA* mutations. Many of these cancers do not express estrogen receptors, which may explain the lack of efficacy in certain cases. Several observational studies have shown that tamoxifen can reduce the risk of contralateral breast cancer in women with *BRCA* mutations who have already been diagnosed with cancer in the other breast.²⁹⁻³¹ However, tamoxifen does not reduce a patient's risk of ovarian cancer, and it may increase her risk of uterine cancer.

Prophylactic bilateral mastectomy is the mainstay of breast cancer prevention in this population. Data from a systematic review suggest that this surgery may prevent the incidence of breast cancer in women with *BRCA*



Shared decision-making is important when treating women with *BRCA* mutations because there is no single correct plan.

➤
Prophylactic bilateral mastectomy may prevent the incidence of breast cancer in women with *BRCA* mutations by 90% to 95%.

TABLE 2

Family history factors suggesting possible *BRCA* mutations²¹

• Breast cancer diagnosis before age 50
• Bilateral breast cancer
• Occurrences of both breast and ovarian cancer
• Tubal and peritoneal cancer
• Breast cancer in ≥ 1 male relatives
• Multiple cases of breast cancer in the extended family
• One or more family members with 2 primary types of <i>BRCA</i> -related cancers
• Ashkenazi Jewish ethnicity

mutations by 90% to 95%.³² However, this review did not demonstrate a reduction in mortality from breast cancer, likely due to poor data quality.³² The National Comprehensive Cancer Network (NCCN) recommends discussing prophylactic mastectomy with all women who have *BRCA* mutations.²⁸ Further conversations are important to review the risk of tissue left behind and quality-of-life issues, including the inability to breastfeed if the woman wants more children and the cosmetic changes with reconstruction.

Ovarian cancer screening and risk-reduction strategies

■ **Screening.** No effective screening strategy has been endorsed for ovarian cancer, as most previous studies have shown screening to be ineffective.^{26,33} Recently, studies both in the United Kingdom and the United States have investigated a screening strategy using the risk-of-ovarian-cancer algorithm (ROCA), which calculates an individual's risk based on serum levels of cancer antigen 125 (CA-125).^{34,35} These studies measured CA-125 levels every 3 to 4 months followed by transvaginal ultrasound if CA-125 increased substantially (as determined by ROCA). Absent an abnormal increase in CA-125, transvaginal ultrasound was performed annually. These screening strategies showed improved specificity over annual screening programs,

and the cancers detected were more likely to be diagnosed at an early stage (stage II vs stage III) and had higher rates of zero residual disease after surgery compared with those detected 1 year after screening ended.^{34,35} However, survival data are not yet available. More research is needed to determine if more frequent screening approaches could improve survival in high-risk women.

NCCN and the American College of Obstetricians and Gynecologists (ACOG) do not endorse routine screening with transvaginal ultrasound and serum CA-125 for high-risk women, as the benefits are uncertain. However, they do advise that these screens may be considered as a short-term strategy for women ages 30 to 35 who defer risk-reducing surgery.^{26,36} The USPSTF does not make a recommendation regarding ovarian cancer screening in high-risk women.³⁷

■ **Risk-reduction strategies.** Risk-reducing bilateral salpingo-oophorectomy (RRSO) is the only recommended technique for reducing the risk of ovarian cancer in women at high risk.^{26,33,36} Meta-analyses have shown an 80% reduction in ovarian cancer risk¹⁶ and 68% reduction in all-cause mortality with this approach.³⁸ The NCCN recommends RRSO for women with a known *BRCA1* mutation between the ages of 35 and 40 who have completed childbearing.³⁶ Since the onset of ovarian cancer tends to be later in women with *BRCA2* mutations, it is reasonable to delay RRSO until age 40 to 45 in this population if they have taken other steps to maximize breast cancer prevention (ie, bilateral mastectomy).³⁶

Adverse effects of RRSO include surgery complications (wound infection, small bowel obstruction, bladder perforation) and effects of early menopause (vasomotor symptoms, decreased sexual functioning, and increased risk of osteoporosis, cardiovascular disease, and all-cause mortality).³⁹⁻⁴¹ In the absence of contraindications, ACOG recommends using hormone therapy in women undergoing RRSO until the natural age of menopause,⁴² particularly if their breast tissue has been removed.

■ **Salpingectomy as an alternative.** In an attempt to reduce these adverse effects of early menopause, and because a large

proportion of high-grade serous tumors originate in the fallopian tube,⁴³ interest has increased in the use of risk-reducing salpingectomy (removal of fallopian tubes) and delayed oophorectomy in women at high risk of ovarian cancer.⁴² Studies have shown this may be a cost-effective approach and an acceptable alternative in *BRCA* mutation carriers who are unwilling to undergo RRSO.^{44,45} A clinical trial investigating this approach in women with *BRCA* mutations is currently underway in the United States.⁴⁶ Many centers offer salpingectomy to high-risk patients < 40 years old, understanding that ovary removal is an eventuality for these patients.

■ When oral contraceptive pills might be beneficial. In younger women with *BRCA* mutations, there may also be a role for oral contraceptive pills (OCPs) as a risk-reducing strategy. Meta-analyses have shown an approximately 50% reduction in the risk of ovarian cancer among women with *BRCA* mutations who use OCPs.⁴⁷⁻⁴⁹

ACOG advises that it is appropriate for women with *BRCA* mutations to use oral contraceptives if indicated (for pregnancy prevention or menstrual cycle regulation), and that it is reasonable to use them for cancer prevention.²⁶ NCCN does not make a formal recommendation, although it does state OCPs may reduce the risk of ovarian cancer in women with a *BRCA* mutation.³⁶ Case-control studies have produced conflicting data on the association between OCP use and breast cancer risk in *BRCA* mutation carriers,⁵⁰⁻⁵³ although 2 meta-analyses found no significant association in this population.^{47,48}

Decision aids for women with *BRCA* mutations

Decision aids are visual displays of risk that help patients work through complex decisions. Most decision aids are in print or digital format and include information about the decision to be made as well as pictorial examples of possible outcomes. Pictographs are especially helpful in communicating information. Some decision aids for women with *BRCA* mutations can be complicated with multiple outcomes (ie, breast cancer and ovarian cancer) and multiple potential inter-

TABLE 3

Screening recommendations for breast cancer in women with *BRCA* mutations^{27,28}

<ul style="list-style-type: none"> • Perform a clinical breast exam every 6-12 months starting at age 25 or at 10 years prior to the earliest breast cancer diagnosis in the family.
<ul style="list-style-type: none"> • Advise annual MRI screening of the breasts with contrast starting at age 25.
<ul style="list-style-type: none"> • Advise annual mammography (in addition to MRI) every 6 months starting at age 30.
<ul style="list-style-type: none"> • Consider advising annual screening with ultrasound if MRI is unavailable.

MRI, magnetic resonance imaging.

ventions (risk-reducing surgery, enhanced screening options).⁵⁴

A Cochrane review found that decision aids increased patients' knowledge, helped patients clarify their values, and may improve value-concordant decisions.⁵⁵ Two papers describing the use of decision aids for women with *BRCA* mutations^{56,57} documented decreased decisional conflict and increased satisfaction.

CASE ►

Ms. T underwent the recommended mammogram and MRI screening for breast cancer, as well as testing with serum CA-125 and ultrasound examinations for ovarian cancer. Her initial mammogram and MRI revealed early stage, triple-negative right breast cancer. She chose to undergo bilateral mastectomy and reconstruction. She has now completed treatment and continues to work closely with her oncology team for appropriate breast follow-up.

One year after her initial diagnosis, at the age of 35, she returned to discuss fertility. She was recently married, and she and her husband wanted to start having children. She was concerned about a safe timeline for her to pursue pregnancy, saying she felt "like a ticking time-bomb" given her prior cancer and carrier status. She wanted to discuss the risks and benefits of pregnancy and when she should consider prophylactic oophorectomy. She had a few options. She could have a baby and then undergo an RRSO, or she could talk to her gynecologist about having a salpingectomy to reduce her risk now and use assisted

reproductive technology to get pregnant. She could also freeze eggs or embryos, have an RRSO, and then use a surrogate to get pregnant. We informed her that pregnancy would not affect her risk of ovarian cancer and discussed the options for pre-implantation genetic testing to assure that her children would not carry the genetic mutation.⁵⁸

We provided Ms. T and her husband with a decision aid to help them navigate the decision. They are currently evaluating the options and said they would let us know when they made a decision. **JFP**

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GUEST EDITORIAL

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We're used to medical consequences for tests that we order—whether a prostate biopsy for an elevated prostate-specific antigen test result, breast biopsy after abnormal mammogram, or a hemoglobin A1C test after an elevated fasting blood sugar. We can handle discussions with patients about potential diagnostic paths and readily include that information as part of shared decision-making with patients. Unfortunately, many entities are increasingly using medical information to make nonmedical decisions.

Using the CAC score to discuss the risk of adverse coronary events with my patients may be appropriate. In nonmedical settings,

however, this data may be incorrectly, unfairly, or dangerously applied to our patients. I've begun thinking about these nonmedical applications as part of the shared decision-making process with my patients. It's making these conversations more complicated, but life and life events for our patients take place far beyond the walls of our exam rooms. **JFP**

References

1. Garner KK, Pomeroy W, Arnold JJ. Exercise stress testing: indications and common questions. *Am Fam Physician.* 2017;96:293-299A.
2. Rose J. It's possible to get life insurance with a high calcium score. Good Financial Cents 2019. www.goodfinancialcents.com/life-insurance-with-a-high-calcium-score/. Last modified February 20, 2019. Accessed May 27, 2020.