Annals of Internal Medicine | Clinical Guideline

# Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement

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**Description:** Update of the 2005 U.S. Preventive Services Task Force (USPSTF) recommendation on genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility.

**Methods:** The USPSTF reviewed the evidence on risk assessment, genetic counseling, and genetic testing for potentially harmful BRCA mutations in asymptomatic women with a family history of breast or ovarian cancer but no personal history of cancer or known potentially harmful BRCA mutations in the family. The USPSTF also reviewed interventions aimed at reducing the risk for BRCA-related cancer in women with potentially harmful BRCA mutations, including intensive cancer screening, medications, and risk-reducing surgery.

**Population:** This recommendation applies to asymptomatic women who have not been diagnosed with BRCA-related cancer.

**Recommendation:** The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (B recommendation)

The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes. (D recommendation)

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* For a list of the members of the USPSTF, see the **Appendix** (available at www.annals.org).

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*The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.*

*It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.*

*The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.*

## Summary of Recommendations and Evidence

The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (B recommendation)

The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes. (D recommendation)

See the Clinical Considerations section for additional information on screening tools.

See the **Figure** for a summary of the recommendation and suggestions for clinical practice.

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***Figure.*** **Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: clinical summary of U.S. Preventive Services Task Force recommendation.**

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U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

## RISK ASSESSMENT, GENETIC COUNSELING, AND GENETIC TESTING FOR BRCA-RELATED CANCER IN WOMEN CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

| | | |
|---|---|---|
| **Population** | Women who have not been diagnosed with BRCA-related cancer and who have no signs or symptoms of the disease | |
| **Recommendation** | Screen women whose family history may be associated with an increased risk for potentially harmful BRCA mutations. Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing.<br>Grade: B | Do not routinely recommend genetic counseling or BRCA testing to women whose family history is not associated with an increased risk for potentially harmful BRCA mutations.<br>Grade: D |

| | | |
|---|---|---|
| **Risk Assessment** | Family history factors associated with increased likelihood of potentially harmful BRCA mutations include breast cancer diagnosis before age 50 years, bilateral breast cancer, family history of breast and ovarian cancer, presence of breast cancer in ≥1 male family member, multiple cases of breast cancer in the family, ≥1 family member with 2 primary types of BRCA-related cancer, and Ashkenazi Jewish ethnicity.<br>Several familial risk stratification tools are available to determine the need for in-depth genetic counseling, such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7. | |
| **Screening Tests** | Genetic risk assessment and BRCA mutation testing are generally multistep processes involving identification of women who may be at increased risk for potentially harmful mutations, followed by genetic counseling by suitably trained health care providers and genetic testing of selected high-risk women when indicated.<br>Tests for BRCA mutations are highly sensitive and specific for known mutations, but interpretation of results is complex and generally requires posttest counseling. | |
| **Treatment** | Interventions in women who are BRCA mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications (e.g., tamoxifen or raloxifene); and risk-reducing surgery (e.g., mastectomy or salpingo-oophorectomy). | |
| **Balance of Benefits and Harms** | In women whose family history is associated with an increased risk for potentially harmful BRCA mutations, the net benefit of genetic testing and early intervention is moderate. | In women whose family history is not associated with an increased risk for potentially harmful BRCA mutations, the net benefit of genetic testing and early intervention ranges from minimal to potentially harmful. |
| **Other Relevant USPSTF Recommendations** | The USPSTF has made recommendations on medications for the reduction of breast cancer risk and screening for ovarian cancer. These recommendations are available at www.uspreventiveservicestaskforce.org. | |

FHS-7 = Family History Screen 7.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

**Appendix Table 1** describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

## RATIONALE

### Importance

The cancer types related to potentially harmful mutations of the BRCA genes are predominantly breast, ovarian, and fallopian tube cancer, although other types are also associated (1). In the general population, 12.3% of women will develop breast cancer during their lifetime and 2.74% will die of the disease, whereas 1.4% of women will develop ovarian cancer and 1.0% will die of the disease (2). A woman's risk for breast cancer increases to 45% to 65% by age 70 years if there are clinically significant mutations in either BRCA gene (3, 4). Mutations in the *BRCA1* gene increase ovarian cancer risk to 39% by age 70 years, and *BRCA2* mutations increase ovarian cancer risk to 10% to 17% by age 70 years (3, 4). In the general population, these mutations occur in an estimated 1 in 300 to 500 women (0.2% to 0.3%) (5–8). In a meta-analysis conducted for the USPSTF, the combined prevalence of

*BRCA1* and *BRCA2* mutations was 2.1% in a general population of Ashkenazi Jewish women (9).

### Detection of Potentially Harmful BRCA Mutations

Genetic risk assessment and BRCA mutation testing is generally a multistep process involving identification of individuals who may be at increased risk for potentially harmful mutations, followed by genetic counseling from suitably trained health care providers and genetic testing of selected high-risk individuals when indicated. Several familial risk stratification tools are clinically useful for selecting patients who should be offered genetic counseling to further determine their candidacy for possible BRCA mutation testing.

### Benefits of Testing for Potentially Harmful BRCA Mutations

For women whose family history is associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, adequate evidence suggests that the benefits of testing for potentially harmful BRCA mutations are moderate.

For women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, there is adequate evidence that the benefits of testing for potentially harmful BRCA mutations are few to none.

### Harms of Detection of Potentially Harmful BRCA Mutations and Early Intervention and Treatment

Adequate evidence suggests that the overall harms of detection of and early intervention for potentially harmful BRCA mutations are small to moderate.

### USPSTF Assessment

For women whose family history is associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, there is moderate certainty that the net benefit of testing for potentially harmful BRCA mutations and early intervention is moderate.

For women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, there is moderate certainty that the net benefit of testing for potentially harmful BRCA mutations and early intervention ranges from minimal to potentially harmful.

## Clinical Considerations

### Patient Population Under Consideration

This recommendation applies to asymptomatic women who have not been diagnosed with BRCA-related cancer.

Women who have 1 or more family members with a known potentially harmful mutation in the *BRCA1* or *BRCA2* genes should be offered genetic counseling and testing.

The USPSTF recognizes the potential importance of further evaluating women who have a diagnosis of breast or ovarian cancer. Some women receive genetic testing as part of a cancer evaluation at the time of diagnosis of breast cancer. The USPSTF did not review the appropriate use of BRCA testing in the evaluation of women who are newly diagnosed with breast cancer. That assessment is part of disease management and is beyond the scope of this recommendation. Women who have been diagnosed with breast cancer in the past and who did not receive BRCA testing as part of their cancer care but have a family history of breast or ovarian cancer should be encouraged to discuss further evaluation with their clinician.

These recommendations do not apply to men, although male family members may be identified for testing during evaluation.

### Family History Screening and Risk Assessment

Mutations in the BRCA genes cluster in families, exhibiting an autosomal dominant pattern of transmission in maternal or paternal lineage. During standard elicitation of family history information from patients, primary care providers should ask about specific types of cancer, primary cancer sites, which family members were affected, relatives with multiple types of primary cancer, and the age at diagnosis and sex of affected family members.

For women who have at least 1 family member with breast, ovarian, or other types of BRCA-related cancer, primary care providers may use 1 of several brief familial risk stratification tools to determine the need for in-depth genetic counseling.

Although several risk tools are available, those evaluated by the USPSTF include the Ontario Family History Assessment Tool (**Table 1**), Manchester Scoring System (**Table 2**), Referral Screening Tool (**Table 3**), Pedigree Assessment Tool (**Table 4**), and Family History Screen 7 (FHS-7) (**Table 5**) (10–19). The Referral Screening Tool (an updated version, the B-RST, is available at www.breastcancergenescreen.org) and FHS-7 are the simplest and quickest to administer. All of these tools seem to be clinically useful predictors of which women should be referred for genetic counseling due to increased risk for potentially harmful BRCA mutations (most sensitivity estimates were >85%), although some models have been evaluated in only 1 study (9, 20). To determine which patients would benefit from BRCA risk assessment, primary care providers should not use general breast cancer risk assessment models (for example, the National Cancer Institute Breast Cancer Risk Assessment Tool, which is based on the Gail model) because they are not designed to determine which women should receive genetic counseling or BRCA testing.

In general, these tools elicit information about factors that are associated with increased likelihood of BRCA mutations. Family history factors associated with increased likelihood of potentially harmful BRCA mutations include breast cancer diagnosis before age 50 years, bilateral breast cancer, presence of breast and ovarian cancer, presence of breast cancer in 1 or more male family members, multiple

*Table 1.* **Ontario Family History Assessment Tool***

| Risk Factor | Points |
|---|---|
| **Breast and ovarian cancer** | |
| Mother | 10 |
| Sibling | 7 |
| Second-/third-degree relative | 5 |
| **Breast cancer relative** | |
| Parent | 4 |
| Sibling | 3 |
| Second-/third-degree relative | 2 |
| Male relative (add to above) | 2 |
| **Breast cancer characteristics** | |
| Onset at age 20–29 y | 6 |
| Onset at age 30–39 y | 4 |
| Onset at age 40–49 y | 2 |
| Premenopausal/perimenopausal | 2 |
| Bilateral/multifocal | 3 |
| **Ovarian cancer relative** | |
| Mother | 7 |
| Sibling | 4 |
| Second-/third-degree relative | 3 |
| **Age at ovarian cancer onset** | |
| <40 y | 6 |
| 40–60 y | 4 |
| >60 y | 2 |
| **Age at prostate cancer onset** | |
| <50 y | 1 |
| **Age at colon cancer onset** | |
| <50 y | 1 |
| **Family total** | |
| Referral† | ≥10 |

* From reference 19.
† Referral with a score of ≥10 corresponds to doubling of lifetime risk for breast cancer (22%).

cases of breast cancer in the family, 1 or more family members with 2 primary types of BRCA-related cancer, and Ashkenazi Jewish ethnicity. The USPSTF recognizes that each risk assessment tool has limitations and found insufficient comparative evidence to recommend one tool over another. The USPSTF also found insufficient evidence to support a specific risk threshold for referral for testing.

## Genetic Counseling

Genetic counseling about BRCA mutation testing may be done by trained health professionals, including trained primary care providers. Several professional organizations describe the skills and training necessary to provide comprehensive genetic counseling. The process of genetic counseling includes detailed kindred analysis and risk assessment for potentially harmful BRCA mutations; education about the possible results of testing and their implications; identification of affected family members who may be preferred candidates for testing; outlining options for screening, risk-reducing medications, or surgery for eligible patients; and follow-up counseling for interpretation of test results.

## BRCA Mutation Testing

Adequate evidence suggests that current genetic sequencing tests can accurately detect BRCA mutations. Testing for BRCA mutations should be done only when an individual has a personal or family history that suggests an inherited cancer susceptibility, when an individual has access to a health professional who is trained to provide genetic counseling and interpret test results, and when test results will aid in decision making. Initial testing of a family member who has breast or ovarian cancer is the preferred strategy in most cases, but it is reasonable to test if no affected relative is available. It is essential that before testing, the individual is fully informed about the implications of testing and has expressed a desire for it.

The type of mutation analysis required depends on family history. Individuals from families with known mutations or from ethnic groups in which certain mutations are more common (for example, Ashkenazi Jewish women) can be tested for these specific mutations.

Individuals without linkages to families or groups with known mutations receive more comprehensive testing. In these cases, when possible, testing should begin with a relative who has breast or ovarian cancer to determine whether affected family members have a clinically significant mutation.

Tests for BRCA mutations are highly sensitive and specific for known mutations, but interpretation of results is complex and generally requires posttest counseling. Test results for genetic mutations are reported as positive (that is, potentially harmful mutation detected), variants of uncertain clinical significance, uninformative-negative, or

*Table 2.* **Manchester Scoring System***

| Risk Factor | *BRCA1* Score | *BRCA2* Score |
|---|---|---|
| **Age at onset of female breast cancer†** | | |
| <30 y | 6 | 5 |
| 30–39 y | 4 | 4 |
| 40–49 y | 3 | 3 |
| 50–59 y | 2 | 2 |
| ≥60 y | 1 | 1 |
| **Age at onset of male breast cancer†** | | |
| <60 y | 5‡ | 8§ |
| ≥60 y | 5‡ | 5§ |
| **Age at onset of ovarian cancer†** | | |
| <60 y | 8 | 5 |
| ≥60 y | 5 | 5 |
| **Pancreatic cancer** | 0 | 1 |
| **Age at onset of prostate cancer†** | | |
| <60 y | 0 | 2 |
| ≥60 y | 0 | 1 |

* From reference 13. Developed so that a score of 10 in either column or a combined score of 15 for both columns would be equivalent to a 10% chance of identifying a *BRCA1* or *BRCA2* mutation.
† For relatives in direct lineage.
‡ If *BRCA2* tested.
§ If *BRCA1* tested.

*Table 3.* **Referral Screening Tool***

| Risk Factor | Breast Cancer at Age ≤50 y | Ovarian Cancer at Any Age |
|---|---|---|
| Yourself | | |
| Mother | | |
| Sister | | |
| Daughter | | |
| Mother's side | | |
| Grandmother | | |
| Aunt | | |
| Father's side | | |
| Grandmother | | |
| Aunt | | |
| ≥2 cases of breast cancer after age 50 y on the same side of the family | | |
| Male breast cancer at any age in any relative | | |
| Jewish ancestry | | |

* From reference 16. A patient completes the checklist if she has a family history of breast or ovarian cancer and receives a referral if she checks ≥2 items.

true-negative. Women who have relatives with known BRCA mutations can be reassured about their inherited risk for a potentially harmful mutation if the results are negative (that is, a true-negative). Some studies suggest increased breast cancer risk in some women with true-negative results (21–24). However, a comprehensive meta-analysis conducted for the USPSTF that included these studies found that breast cancer risk is generally not increased in women with true-negative results (9). An uninformative-negative result occurs when a woman's test does not detect a potentially harmful mutation but no relatives have been tested or no mutations have been detected in tested relatives. Available tests may not be able to identify mutations in these families. Risk for breast cancer is increased in women with uninformative-negative results (9).

### Timing of Screening

Consideration of screening for potentially harmful BRCA mutations should begin once women have reached the age of consent (18 years). Primary care providers should periodically assess all patients for changes in family history (for example, comprehensive review at least every 5 to 10 years [25]).

### Interventions for Women Who Are BRCA Mutation Carriers

Interventions that may reduce risk for cancer or cancer-related death in women who are BRCA mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications (for example, tamoxifen or raloxifene); and risk-reducing surgery (for example, mastectomy or salpingo-oophorectomy). However, the strength of evidence varies across the types of interventions.

Evidence is lacking on the effect of intensive screening for BRCA-related cancer on clinical outcomes in women who are BRCA mutation carriers. Medications, such as tamoxifen and raloxifene, have been shown to reduce the incidence of invasive breast cancer in high-risk women in the general population, but they have not been studied specifically in women who are BRCA mutation carriers (9, 20, 26).

In high-risk women and those who are BRCA mutation carriers, cohort studies of risk-reducing surgery (mastectomy and salpingo-oophorectomy) showed substantially reduced risk for breast or ovarian cancer. Breast cancer risk was reduced by 85% to 100% with mastectomy (27–29) and by 37% to 100% with oophorectomy, and ovarian cancer risk was reduced by 69% to 100% with oophorectomy or salpingo-oophorectomy (26). Salpingo-oophorectomy was also associated with a 55% relative reduction in all-cause mortality (as measured during the course of the study) in women with *BRCA1* or *BRCA2* mutations and without a history of breast cancer (27).

### Other Approaches to Prevention

The USPSTF recommendations on medications for breast cancer risk reduction are available on the USPSTF Web site (www.uspreventiveservicestaskforce.org).

The USPSTF recommends against screening for ovarian cancer in women. This recommendation does not apply to women with known genetic mutations that increase their risk for ovarian cancer (for example, BRCA mutations).

### Useful Resources

The National Cancer Institute Cancer Genetics Services Directory provides a list of professionals who offer services related to cancer genetics, including cancer risk assessment, genetic counseling, and genetic susceptibility testing (available at http://www.cancer.gov/cancertopics/genetics/directory).

## Other Considerations

Although some studies have reported that women prefer in-person genetic counseling, telephone- or computer-based counseling may be considered for women who would not otherwise have access to these services.

### Research Needs and Gaps

Research on risk assessment and testing for BRCA mutations has focused on short-term outcomes for highly selected women in referral centers. Additional studies are

*Table 4.* **Pedigree Assessment Tool***

| Risk Factor | Score† |
|---|---|
| Breast cancer at age ≥50 y | 3 |
| Breast cancer at age <50 y | 4 |
| Ovarian cancer at any age | 5 |
| Male breast cancer at any age | 8 |
| Ashkenazi Jewish heritage | 4 |

* From reference 17. A score of ≥8 is the optimum referral threshold.
† For every family member with a diagnosis of breast or ovarian cancer, including second- or third-degree relatives.

*Table 5.* **Family History Screen-7***

| |
|---|
| Did any of your first-degree relatives have breast or ovarian cancer? |
| Did any of your relatives have bilateral breast cancer? |
| Did any man in your family have breast cancer? |
| Did any woman in your family have breast and ovarian cancer? |
| Did any woman in your family have breast cancer before age 50 y? |
| Do you have 2 or more relatives with breast and/or ovarian cancer? |
| Do you have 2 or more relatives with breast and/or bowel cancer? |

* From reference 18. One positive response initiates referral.

needed, including comparative effectiveness trials of approaches to risk screening and strategies to improve access to genetic counseling and BRCA testing for high-risk individuals.

Another unresolved question is what specific training is needed (for persons other than trained genetic counselors) to provide genetic counseling. It would be helpful to understand which methods of delivery of genetic counseling are most effective, including those that can increase access to genetic counseling in rural or other settings. Trials comparing types of providers and protocols could address these questions.

What happens after patients are identified as high-risk in clinical settings is unknown. The consequences of genetic testing for individuals and their relatives require more study. Well-designed investigations using standardized measures and diverse study populations are needed.

An expanded database or registry of patients receiving genetic counseling for inherited breast and ovarian cancer susceptibility or who are tested for BRCA mutations would provide useful information about predictors of cancer and response to interventions. Additional data are needed from women of varying socioeconomic, racial, and ethnic groups.

For women who are mutation carriers, studies about the effectiveness of intensive cancer screening and risk-reducing medications and the effects of age at intervention on improving long-term outcomes are needed. This research would increase knowledge of the relative benefits and harms of interventions that are provided on the basis of genetic risk information.

## DISCUSSION

### Burden of Disease

Breast cancer is the second most common cancer in women in the United States and is the second leading cause of cancer death (30, 31). In 2013, an estimated 232 340 women in the United States will be diagnosed with breast cancer and 39 620 women will die of the disease (32). According to lifetime risk estimates for the general population, 12.3% of women will develop breast cancer during their lives and 2.74% will die of it (2).

Ovarian cancer is the fifth leading cause of cancer death in women in the United States (31), accounting for an estimated 22 240 new cases and 14 030 deaths in 2013 (33). According to lifetime risk estimates for the general population, 1.4% of women will develop ovarian cancer during their lives and 1.0% will die of it (2).

Estimates of the prevalence of potentially harmful BRCA mutations vary by population. The estimated prevalence is 0.2% to 0.3% in the general population of women (5–8), 6.0% in women with cancer onset before age 40 years (8, 34, 35), and 2.1% in the general population of Ashkenazi Jewish women (36–39). In a meta-analysis of studies in which recruitment was based on family history of breast or ovarian cancer, *BRCA1* mutation prevalence was 13.6%, *BRCA2* mutation prevalence was 7.9%, and prevalence of either mutation was 19.8% (9).

### Scope of Review

This recommendation applies to women who have no signs or symptoms of BRCA-related cancer. For its updated evidence review, the USPSTF considered risk assessment, genetic counseling, and genetic testing for potentially harmful *BRCA1* or *BRCA2* mutations in asymptomatic women with a family history of breast or ovarian cancer but no personal history of cancer or known potentially harmful BRCA mutations in their family. The USPSTF also reviewed interventions aimed at reducing the risk for BRCA-related cancer in women with potentially harmful BRCA mutations, including intensive cancer screening (for example, earlier and more frequent mammography or magnetic resonance imaging of the breast), medications (for example, tamoxifen or raloxifene), and risk-reducing surgery (for example, mastectomy or oophorectomy). Studies about patients with current or past breast or ovarian cancer were excluded unless they were designed to address screening issues in women without cancer (for example, retrospective or case–control studies).

### Accuracy of Familial Risk Assessment

The USPSTF reviewed several tools that could be used in primary care settings to predict individual risk for breast cancer and potentially harmful BRCA mutations.

Tools specifically designed to determine risk for BRCA-related cancer are primarily intended for use by nongeneticist health care providers to guide referral to genetic counselors for more definitive evaluation. Models that have been validated in studies include the Ontario Family History Assessment Tool (**Table 1**), Manchester Scoring System (**Table 2**), Referral Screening Tool (**Table 3**), Pedigree Assessment Tool (**Table 4**), and FHS-7 (**Table 5**) (10–19). In general, these tools elicit information about factors associated with increased likelihood of BRCA mutations. They are clinically useful predictors of which women should be referred for genetic counseling because of increased risk for potentially harmful BRCA mutations (most sensitivity estimates were >85%), although some models have been evaluated in only 1 study (9, 20). The USPSTF recognizes that each risk assessment tool has lim-

itations and found insufficient evidence to recommend one tool over another.

### Accuracy of BRCA Mutation Testing

The type of mutation analysis done depends on family history. Individuals from families with known mutations or from ethnic groups with common mutations (for example, Ashkenazi Jewish women) can be tested specifically for these mutations. The sensitivity and specificity of analysis techniques are measured by individual clinical laboratories and are not publicly available. Individuals without linkages to families or groups with known mutations receive more comprehensive testing. In these cases, guidelines recommend initial testing of a relative with known breast or ovarian cancer, when possible, to check for the presence of clinically significant mutations.

### Effectiveness of BRCA Mutation Testing and Early Detection and Treatment

To understand the potential benefits and harms of genetic counseling, the USPSTF reviewed 18 studies (40–57) published since its previous review. Studies generally reported positive (or no negative) psychological effects, increased accuracy of risk perception, or decreased intention to have genetic testing.

Genetic counseling significantly decreased breast cancer worry in 8 studies (44–46, 48, 50, 53–55). Three studies (41, 44, 49) reported decreased or no changes in general anxiety and depression after genetic counseling, whereas other studies found no significant differences in anxiety scores (48, 50). However, 1 of these studies noted an increase in state anxiety scores after genetic counseling (44). Eight studies published since 2004 reported improved accuracy of risk perception after genetic counseling (41, 42, 44–47, 49, 50, 52). Two studies reported decreased intention to have genetic testing after genetic counseling (45, 46).

Interventions that may reduce risk for cancer in women who are BRCA mutation carriers include earlier, more frequent, or intensive cancer screening; use of selective estrogen-receptor modulators as risk-reducing medications (for example, tamoxifen or raloxifene); and risk-reducing surgery (for example, mastectomy or salpingo-oophorectomy).

Evidence is lacking on the effect of intensive screening for BRCA-related cancer on clinical outcomes in women who are BRCA mutation carriers.

Selective estrogen-receptor modulators reduced the incidence of invasive breast cancer in several randomized, controlled trials (58–64), although clinical trials of tamoxifen and raloxifene have not been conducted specifically in women who are BRCA mutation carriers. In a meta-analysis of trials published to date (26, 65), tamoxifen and raloxifene reduced the incidence of estrogen-receptor–positive invasive breast cancer, with 7 fewer events per 1000 women for tamoxifen (4 trials) and 9 fewer events per 1000 women for raloxifene (2 trials), assuming 5 years of treatment. Selective estrogen-receptor modulators do not reduce risk for estrogen-receptor–negative breast cancer, which includes 69% of breast cancer cases associated with *BRCA1* mutations and 16% associated with *BRCA2* mutations (66).

In cohort studies of high-risk women and those who are BRCA mutation carriers, risk-reducing surgery (for example, mastectomy or salpingo-oophorectomy) substantially reduced risk for breast or ovarian cancer. Mastectomy reduced breast cancer risk by 85% to 100%, and oophorectomy or salpingo-oophorectomy reduced ovarian cancer risk by 69% to 100% and breast cancer risk by 37% to 100% (9). In 1 fair-quality prospective cohort study (27), salpingo-oophorectomy was also associated with a 55% relative reduction in all-cause mortality (as measured during the course of the study) in women with *BRCA1* and *BRCA2* mutations without a history of breast cancer. Breast cancer risk reduction associated with oophorectomy was more pronounced in women who were premenopausal at the time of surgery (27, 67).

### Potential Harms of Cancer Screening and Treatment

Intensive screening for breast and ovarian cancer is associated with false-positive results, unnecessary imaging, and unneeded surgery. In 2 studies comparing mammography with magnetic resonance imaging for breast cancer screening in which 18% to 100% of study participants were BRCA mutation carriers, mammography was associated with higher false-positive rates (14% vs. 5.5% in the first round of screening; $P < 0.001$ [68]; 15% vs. 11% in another study [69]) and more false-negative results (12 vs. 1 case in the first round of screening; 12 vs. 4 cases in subsequent rounds [68]). In a retrospective analysis of a cohort of women with potentially harmful BRCA mutations or first-degree relatives with BRCA mutations, those who were screened with mammography were more likely to have unneeded imaging than those who were screened with magnetic resonance imaging; however, rates of unneeded biopsy were similar (69).

Risk-reducing medications (for example, tamoxifen or raloxifene) can increase risk for thromboembolic events (4 to 7 events per 1000 women over 5 years). Tamoxifen increased the risk for endometrial cancer (4 to 5 cases per 1000 women) compared with placebo or raloxifene, and it also increased risk for cataracts (15 per 1000 women) compared with raloxifene (26, 63).

Data on the long-term physical harms of risk-reducing mastectomy are limited. In high-risk women having risk-reducing mastectomy with immediate reconstruction, 21% in 1 series had complications (for example, hematoma, contracture, or implant rupture) (70). In another series, 64% reported postsurgical symptoms (for example, numbness, pain, tingling, infection, swelling, breast hardness, bleeding, organizing hematoma, failed reconstruction, breathing problems, thrombosis, and pulmonary embolism) (71). After risk-reducing oophorectomy, 5% of

women in 1 study had postsurgical complications (for example, wound infection, bladder or uterine perforation, or small-bowel obstruction) (72).

Seven observational studies provided data on psychological distress due to risk-reducing mastectomy (71, 73–76) or oophorectomy (25, 77). In 1 study of 90 women who had risk-reducing bilateral mastectomy (73, 74), there were significant reductions in scores for anxiety and sexual pleasure and no significant differences in depression scores, body image concerns, or other measures. In another study (75), there were no significant differences in psychological measures between women who had risk-reducing mastectomy and a reference sample that did not have the procedure. Ten years after risk-reducing mastectomy, most women in another study reported that their family lives were unchanged, but 39% reported negative effects on spousal relationships because of decreased sensation and changed body appearance (76). After risk-reducing salpingo-oophorectomy, premenopausal women reported significant worsening of vasomotor symptoms and decreased sexual function (77).

### Estimate of Magnitude of Net Benefit

For women whose family history is associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, the USPSTF found adequate evidence that the benefits of testing, detection, and early intervention are moderate. For women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, the USPSTF found adequate evidence that the benefits of testing, detection, and early intervention are few to none. The USPSTF found adequate evidence that the overall harms of testing, detection, and early intervention are small to moderate.

For women whose family history is associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, the USPSTF concludes with moderate certainty that the net benefit of testing, detection, and early intervention is moderate. For women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes, the USPSTF concludes with moderate certainty that the net benefit of testing, detection, and early intervention ranges from minimal to potentially harmful.

### How Does Evidence Fit With Biological Understanding?

The *BRCA1* and *BRCA2* genes are tumor-suppressor genes. Mutations of these genes have been linked to hereditary breast and ovarian cancer. Risks for breast, ovarian, and other types of BRCA-related cancer are greatly increased in patients who have inherited potentially harmful *BRCA1* or *BRCA2* mutations. Genetic testing may identify such mutations. Several options are available to manage cancer risk in patients who are found to be mutation carriers.

### Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 2 April through 29 April 2013. In response to comments, the USPSTF clarified that this recommendation statement applies to women. It also expanded the recommendation to include women who have family members with tubal or peritoneal (in addition to breast or ovarian) cancer. The USPSTF clarified that it recognizes the potential importance of further evaluating women who have a diagnosis of breast or ovarian cancer; however, that assessment is part of disease management and is beyond the scope of this recommendation.

The USPSTF added that it found insufficient evidence to recommend one risk assessment tool over another or to support a specific risk threshold for referral for genetic counseling and BRCA testing. It also added a compilation of risk assessment tools (**Tables 1** to **5**). Although the preferred BRCA testing strategy is initial testing of a family member with breast or ovarian cancer, the USPSTF clarified that it is reasonable to start testing in an unaffected individual if no affected relative is available. Because of the complexity of BRCA test results, the USPSTF also suggests posttest counseling. It also clarified and updated information on BRCA testing, other resources, and recommendations of other groups.

## Update of Previous USPSTF Recommendation

In 2005, the USPSTF recommended that women whose family history is associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for BRCA testing. It also recommended against routine referral for genetic counseling or routine BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes (78).

This recommendation statement reaffirms the USPSTF's previous recommendation. Since 2005, family history risk stratification tools have been developed and validated for use in primary care practice to guide referral for BRCA genetic counseling (**Tables 1** to **5**). In addition, the potential benefits and harms of medications for breast cancer risk reduction have been studied for longer follow-up periods, and more information is available about the potential psychological effects of genetic counseling and risk-reducing surgery.

## Recommendations of Other Groups

The National Comprehensive Cancer Network provides specific criteria for genetic counseling and testing (1). The American Congress of Obstetricians and Gynecologists recommends genetic risk assessment for women who have more than a 20% to 25% risk for an inherited predisposition to breast and ovarian cancer and states that it

may be helpful for patients with more than a 5% to 10% risk (79). The American Society of Clinical Oncology recommends genetic testing when there is a personal or family history suggestive of genetic cancer susceptibility, the test can be adequately interpreted, and the results will aid in diagnosis or medical management of the patient or family member who has hereditary risk for cancer. It also recommends genetic testing only when pretest and posttest counseling are included (80). The National Society of Genetic Counselors has issued practice guidelines for risk assessment and genetic counseling for hereditary breast and ovarian cancer. It recommends offering genetic testing to individuals with a personal or family history suggestive of an inherited cancer syndrome, if the test can be adequately interpreted, if testing will influence medical management of the patient or relative, if potential benefits outweigh potential risks, if testing is voluntary, and if the individual seeking testing or a legal proxy can provide informed consent (81). The European Society for Medical Oncology recommends that all patients who may be referred for BRCA testing first complete informed consent and genetic counseling and that those who are mutation carriers be encouraged to advise close family members to obtain genetic counseling (82). The Society of Gynecologic Oncologists recommends genetic risk assessment for individuals with a personal risk of more than approximately 20% to 25% for an inherited predisposition to cancer and states that it may be helpful for patients with more than approximately 5% to 10% risk. Genetic testing for cancer predisposition requires informed consent that should encompass pretest education and counseling about the risks, benefits, and limitations of testing, including the implications of both positive and negative genetic test results (83).

From the U.S. Preventive Services Task Force, Rockville, Maryland.



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**Requests for Single Reprints:** Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

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## Appendix: U.S. Preventive Services Task Force

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Virginia A. Moyer, MD, MPH, *Chair* (American Board of Pediatrics, Chapel Hill, North Carolina); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas); Francisco A.R. García, MD, MPH (Pima County Department of Health, Tucson, Arizona); Adelita Gonzales Cantu, RN, PhD (University of Texas Health Science Center, San Antonio, Texas); David C. Grossman, MD, MPH (Group Health Cooperative, Seattle, Washington); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Wanda K. Nicholson, MD, MPH, MBA (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Douglas K. Owens, MD, MS (Veterans Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina).

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/members.htm.

*Appendix Table 1.* **What the USPSTF Grades Mean and Suggestions for Practice**

| Grade | Definition | Suggestions for Practice |
|---|---|---|
| A | The USPSTF recommends the service. There is high certainty that the net benefit is substantial. | Offer/provide this service. |
| B | The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. | Offer/provide this service. |
| C | The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small. | Offer/provide this service for selected patients depending on individual circumstances. |
| D | The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. | Discourage the use of this service. |
| I statement | The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. | Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms. |

*Appendix Table 2.* **USPSTF Levels of Certainty Regarding Net Benefit**

| Level of Certainty* | Description |
|---|---|
| High | The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies. |
| Moderate | The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as:<br>the number, size, or quality of individual studies;<br>inconsistency of findings across individual studies;<br>limited generalizability of findings to routine primary care practice; and<br>lack of coherence in the chain of evidence.<br>As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion. |
| Low | The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of:<br>the limited number or size of studies;<br>important flaws in study design or methods;<br>inconsistency of findings across individual studies;<br>gaps in the chain of evidence;<br>findings that are not generalizable to routine primary care practice; and<br>a lack of information on important health outcomes.<br>More information may allow an estimation of effects on health outcomes. |

* The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.