JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer

US Preventive Services Task Force Recommendation Statement

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IMPORTANCE Potentially harmful mutations of the breast cancer susceptibility 1 and 2 genes (*BRCA1/2*) are associated with increased risk for breast, ovarian, fallopian tube, and peritoneal cancer. For women in the United States, breast cancer is the most common cancer after nonmelanoma skin cancer and the second leading cause of cancer death. In the general population, *BRCA1/2* mutations occur in an estimated 1 in 300 to 500 women and account for 5% to 10% of breast cancer cases and 15% of ovarian cancer cases.

OBJECTIVE To update the 2013 US Preventive Services Task Force (USPSTF) recommendation on risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer.

EVIDENCE REVIEW The USPSTF reviewed the evidence on risk assessment, genetic counseling, and genetic testing for potentially harmful *BRCA1/2* mutations in asymptomatic women who have never been diagnosed with *BRCA*-related cancer, as well as those with a previous diagnosis of breast, ovarian, tubal, or peritoneal cancer who have completed treatment and are considered cancer free. In addition, the USPSTF reviewed interventions to reduce the risk for breast, ovarian, tubal, or peritoneal cancer in women with potentially harmful *BRCA1/2* mutations, including intensive cancer screening, medications, and risk-reducing surgery.

FINDINGS For women whose family or personal history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes, or who have an ancestry associated with *BRCA1/2* gene mutations, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are moderate. For women whose personal or family history or ancestry is not associated with an increased risk for harmful mutations in the *BRCA1/2* genes, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are small to none. Regardless of family or personal history, the USPSTF found adequate evidence that the overall harms of risk assessment, genetic counseling, genetic testing, and interventions are small to moderate.

CONCLUSIONS AND RECOMMENDATION The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing. (B recommendation) The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations. (D recommendation)

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The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious 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 clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (*BRCA1/2*) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (B recommendation) (**Figure 1**).

The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations. (D recommendation)

Rationale

Importance

Potentially harmful mutations of the *BRCA1/2* genes are associated with increased risk for breast, ovarian, fallopian tube, and peritoneal cancer.[1-6] For women in the United States, breast cancer is the most common cancer after nonmelanoma skin cancer and the second leading cause of cancer death.[7] In the general population, *BRCA1/2* mutations occur in an estimated 1 in 300 to 500 women and account for 5% to 10% of breast cancer cases and 15% of ovarian cancer cases.[8-11] A woman's risk for breast cancer increases if she has clinically significant mutations in the *BRCA1/2* genes.[12,13] Mutations in the *BRCA1/2* genes increase breast cancer risk to 45% to 65% by age 70 years. Risk of ovarian, fallopian tube, or peritoneal cancer increases to 39% for *BRCA1* mutations and 10% to 17% for *BRCA2* mutations.[12,13]

Detection

Genetic risk assessment and *BRCA1/2* mutation testing is a multistep process that begins with identifying patients with family or personal histories of breast, ovarian, tubal, or peritoneal cancer; family members with known harmful *BRCA1/2* mutations; or ancestry associated with harmful *BRCA1/2* mutations. Risk for clinically significant *BRCA1/2* mutations can be further evaluated with genetic counseling by suitably trained health care clinicians, followed by genetic testing of selected high-risk individuals and posttest counseling about results. The USPSTF found adequate evidence that familial risk assessment tools are accurate in identifying women with increased likelihood of *BRCA1/2* mutations. These tools can be used by primary care clinicians to guide referrals to genetic counseling.

The USPSTF has previously established that there is adequate evidence that current genetic tests can accurately detect known *BRCA1/2* mutations.[14]

Benefits of Screening, Genetic Counseling, and Genetic Testing

The USPSTF found adequate evidence that the benefits of risk assessment, genetic counseling, and genetic testing are moderate in women whose family history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes.

The USPSTF found adequate evidence that the benefits of risk assessment, genetic counseling, and genetic testing are small to none in women whose family history is not associated with an increased risk for harmful mutations in the *BRCA1/2* genes.

Harms of Screening, Genetic Counseling, and Genetic Testing

The USPSTF found adequate evidence that the harms associated with risk assessment, genetic counseling, genetic testing, and interventions are small to moderate.

USPSTF Assessment

The USPSTF concludes with moderate certainty that the net benefit of risk assessment for increased risk of *BRCA1/2* mutations, testing for *BRCA1/2* mutations, and use of risk-reducing interventions outweighs the harms in women whose family or personal history is associated with an increased risk for potentially harmful mutations in the *BRCA1/2* genes.

The USPSTF concludes with moderate certainty that the harms of risk assessment for increased risk of *BRCA1/2* mutations, testing for *BRCA1/2* mutations, and use of risk-reducing interventions outweigh the benefits in women whose family or personal history is not associated with an increased risk for potentially harmful mutations in the *BRCA1/2* genes.

Clinical Considerations

Patient Population Under Consideration

This recommendation applies to women who are asymptomatic for *BRCA*-related cancer and have unknown *BRCA* mutation status (**Figure 2**). It includes women who have never been diagnosed with *BRCA*-related cancer, as well as those with a previous breast, ovarian, tubal, or peritoneal cancer diagnosis who have completed treatment and are considered cancer free but have not been previously tested. While this recommendation applies to women, the net benefit estimates are driven by biological sex (ie, male/female) rather than gender identity. Persons should consider their sex at birth to determine which recommendation best applies to them.

Assessment of Risk

Mutations in the *BRCA1/2* genes cluster in families, showing an autosomal dominant pattern of inheritance in either the mother's or father's family. When taking medical and family history information from patients, primary care clinicians should ask about specific types of cancer, primary cancer sites, which family members were

Figure 1. USPSTF Grades and Levels of Evidence

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 or 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 or 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 or 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.

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 the number, size, or quality of individual studies. inconsistency of findings across individual studies. limited generalizability of findings to routine primary care practice. lack of coherence in the chain of evidence. 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 the limited number or size of studies. important flaws in study design or methods. inconsistency of findings across individual studies. gaps in the chain of evidence. findings not generalizable to routine primary care practice. lack of information on important health outcomes. More information may allow 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 based on the nature of the overall evidence available to assess the net benefit of a preventive service.	

USPSTF indicates US Preventive Services Task Force.

affected, and whether relatives had multiple types of primary cancer. Clinicians should also inquire about the age at diagnosis, age at death, and sex of affected family members, both immediate (ie, parents and siblings) as well as more distant (ie, aunts, uncles, grandparents, and cousins).

For women who have family members with breast, ovarian, tubal, or peritoneal cancer or have a personal history of these types of cancer, primary care clinicians may use appropriate brief familial risk assessment tools to determine the need for in-depth genetic counseling. Tools 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**), 7-Question Family History Screening Tool (**Table 5**), International Breast Cancer Intervention Study instrument (Tyrer-Cuzick) (**Table 6**), and brief versions of BRCAPRO. Each of these tools has been validated and accurately estimate the likelihood of carrying a harmful *BRCA1/2* mutation. They can be used to guide referrals to genetic counseling for more definitive risk assessment.[28] General breast cancer risk assessment models (eg, the National Cancer Institute Breast Cancer Risk Assessment Tool, which is based on the Gail model) are not designed to identify *BRCA*-related cancer risk and should not be used for this purpose.

In general, these brief familial risk assessment tools include factors associated with increased likelihood of potentially harmful

Figure 2. Clinical Summary: Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer

Population	Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutations	Women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations
Recommendation	Assess with an appropriate brief familial risk assessment tool. Grade: B	Do not perform routine risk assessment, genetic counseling, or genetic testing. Grade: D

Risk Assessment	Patients with family or personal histories of breast, ovarian, tubal, or peritoneal cancer or ancestry associated with harmful *BRCA1/2* mutations should be assessed using a familial risk assessment tool. The USPSTF found adequate evidence that these tools are accurate in identifying women with increased likelihood of *BRCA1/2* mutations. Tools evaluated by the USPSTF include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), and brief versions of BRCAPRO. These tools should be used to guide referrals to genetic counseling.
Genetic Counseling	Genetic counseling about *BRCA1/2* mutation testing should be performed by trained health professionals, including suitably trained primary care providers. The process of genetic counseling includes detailed kindred analysis and risk assessment for potentially harmful *BRCA1/2* mutations. It also includes identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing, and discussion of management options.
Genetic Testing	Tests for *BRCA1/2* mutations are highly sensitive and specific for known mutations. Testing for *BRCA1/2* mutations should be performed when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to see a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision making.
Treatment and Interventions	In general, the care of women with harmful *BRCA1/2* mutations is managed with a variety of interventions to lower future cancer risk. This includes intensive screening, risk-reducing medications, and risk-reducing mastectomy and salpingo-oophorectomy.
Relevant USPSTF Recommendations	The USPSTF recommends that clinicians offer to prescribe risk-reducing medications such as tamoxifen, raloxifene, or aromatase inhibitors to women at increased risk for breast cancer and at low risk for adverse medication effects. It recommends against the routine use of medications for risk reduction of primary breast cancer in women not at increased risk for breast cancer. 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 (eg, *BRCA1/2* mutations). The USPSTF found insufficient evidence to assess the balance of benefits and harms of performing screening pelvic examinations in asymptomatic women for the early detection and treatment of a range of gynecologic conditions.

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

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BRCA indicates breast cancer susceptibility gene; USPSTF, US Preventive Services Task Force.

BRCA1/2 mutations. These include breast cancer diagnosis before age 50 years, bilateral breast cancer, presence of both breast and ovarian cancer in one individual, male family members with breast cancer, multiple cases of breast cancer in the family, 1 or more family members with 2 primary types of *BRCA*-related cancer (such as ovarian cancer), and Ashkenazi Jewish ancestry. The USPSTF recognizes that each risk assessment tool has advantages and limitations and found insufficient evidence to recommend one over another.

Genetic Counseling

The process of genetic counseling includes detailed kindred analysis and risk assessment for potentially harmful *BRCA1/2* mutations. It also includes identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing, and discussion of management options. Genetic counseling about *BRCA1/2* mutation testing should be performed by trained health professionals, including suitably trained primary care clinicians. Several professional organizations describe the skills and training necessary to provide comprehensive genetic counseling.

Genetic Testing

Testing for *BRCA1/2* mutations should be performed only when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to talk with a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision-making. Clinical practice guidelines recommend that *BRCA1/2* mutation testing begin with a relative with known *BRCA*-related cancer, including male relatives, to determine if a clinically significant mutation is detected in the family before testing individuals without cancer.[29] If an affected family member with a *BRCA*-related cancer is not available, then the relative with the highest probability of

Table 1. Ontario Family History Assessment Tool[a]

Risk Factor	Points
Breast and ovarian cancer	
Mother	10
Sibling	7
Second-/third-degree relative	5
Breast cancer relatives	
Parent	4
Sibling	3
Second-/third-degree relative	2
Male relative (add to above)	2
Breast cancer characteristics	
Onset age, y	
20-29	6
30-39	4
40-49	2
Premenopausal/perimenopausal	2
Bilateral/multifocal	3
Ovarian cancer relatives	
Mother	7
Sibling	4
Second-/third-degree relative	3
Ovarian cancer onset age, y	
<40	6
40-60	4
>60	2
Prostate cancer onset	
Age <50 y	1
Colon cancer onset	
Age <50 y	1
Family total	
Referral[b]	≥10

[a] See Gilpin et al,[15] Oros et al,[16] Panchal et al,[17] Parmigiani et al.[18]

[b] Referral with score of 10 or greater corresponds to doubling of lifetime risk for breast cancer (22%).

Table 2. Manchester Scoring System[a,b]

Risk Factor (Age at Onset for Relative in Direct Lineage)	*BRCA1* Score	*BRCA2* Score
Female breast cancer, y		
<30	6	5
30-39	4	4
40-49	3	3
50-59	2	2
≥60	1	1
Male breast cancer, y		
<60	5[c]	8[d]
≥60	5[c]	5[d]
Ovarian cancer, y		
<60	8	5
≥60	5	5
Pancreatic cancer		
Any age	0	1
Prostate cancer, y		
<60	0	2
≥60	0	1
Total individual genes	10	10
Total for combined = 15		

Abbreviation: *BRCA*, breast cancer susceptibility gene.

[a] See Oros et al,[16] Parmigiani et al,[18] Antoniou et al,[19] Barcenas et al,[20] Evans et al.[21]

[b] 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.

[c] If testing for *BRCA2*.

[d] If testing for *BRCA1*.

mutation should be tested. The type of mutation analysis required depends on family history. Individuals from families with known mutations or from ancestry groups in which certain mutations are more common (eg, Ashkenazi Jewish founder mutations) can be tested for these specific mutations. Because risk assessment is primarily based on family history, it is unclear how women with a limited or unknown family history should be assessed for *BRCA1/2* mutation risk and potential referral to counseling or genetic testing.

Tests for *BRCA1/2* mutations are highly sensitive and specific for known mutations. The availability of testing options has changed since the 2013 US Supreme Court ruling that determined human genes are not patentable (*Association for Molecular Pathology et al v Myriad Genetics Inc et al*).[30] Previously, *BRCA1/2* mutation testing in the United States was mainly conducted by 1 laboratory. Since the ruling, the number of testing options has significantly increased, with more than 80 multigene panels that include *BRCA1/2*, as well as tests marketed directly to consumers.[31]

Guidelines from the American College of Medical Genetics and Genomics, which were updated in 2015, recommend new standard terminology for reporting *BRCA1/2* mutations identified by genetic tests. These include a 5-tier terminology system using the terms "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign."[32]

Treatment and Interventions

Management of increased cancer risk related to *BRCA1/2* mutations is beyond the scope of this Recommendation Statement. In general, care for women with harmful *BRCA1/2* mutations consists of a variety of interventions to lower future cancer risk. This includes intensive screening, risk-reducing medications, and risk-reducing mastectomy and salpingo-oophorectomy.

Additional Tools and 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 testing.[33]

Other Related USPSTF Recommendations

The USPSTF recommends that clinicians offer to prescribe risk-reducing medications such as tamoxifen, raloxifene, or aromatase inhibitors to women at increased risk for breast cancer and at low

risk for adverse medication effects (B recommendation). It recommends against the routine use of medications for risk reduction of primary breast cancer in women not at increased risk for breast cancer (D recommendation).[34]

The USPSTF recommends against screening for ovarian cancer in women (D recommendation). This recommendation does not apply to women with known genetic mutations that increase their risk for ovarian cancer (eg, *BRCA1/2* mutations).[35] The USPSTF found insufficient evidence to assess the balance of benefits and harms of performing screening pelvic examinations in asymptomatic women for the early detection and treatment of a range of gynecologic conditions (I statement).[36]

Other Considerations

Research Needs and Gaps

Research on risk assessment and testing for *BRCA1/2* mutations has focused on short-term outcomes for highly selected women in referral centers. To determine the best approaches for population-based risk assessment and testing, more research is needed about mutation prevalence and effects on the general population as well as ethnicities or ancestries associated with *BRCA1/2* mutations. Because risk assessment is primarily based on family history, more research is needed to better understand how women with an unknown family history should be assessed for *BRCA1/2* mutation risk. Additional studies are needed, including comparative effectiveness trials, of approaches to risk screening and strategies to improve access to genetic counseling, as well as *BRCA1/2* testing for high-risk individuals.

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 with limited access. Trials comparing types of clinicians and protocols could address these questions. 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 *BRCA1/2* mutations would provide useful information about predictors of cancer and response to interventions. Additional data are needed from women of varying socioeconomic and racial/ethnic groups.

For women who are *BRCA1/2* 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

For women, breast cancer is the most common cancer in the United States after nonmelanoma skin cancer and the second leading cause of cancer death.[37] In 2017, an estimated 252 710 women were diagnosed with breast cancer in the United States and 40 610 died of the disease.[37] Ovarian cancer is the fifth leading cause of cancer death in women in the United States.[37] In 2017, an estimated 22 440 women were diagnosed with ovarian cancer and 14 080 died of the disease.[37] Mutations of the *BRCA1/2* genes are estimated to occur in 1 in 300 to 500 women in the general population[8-11] and account for 5% to 10% of breast cancer cases and 15% of ovarian cancer cases.[9,11,38]

Estimates of the prevalence of potentially harmful *BRCA1/2* mutations vary by population. The estimated prevalence is 0.2% to 0.3% in the general population of women, 6.0% in women with cancer onset before age 40 years, and 2.1% in the general population of Ashkenazi Jewish women.[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%.[39]

Table 3. Referral Screening Tool[a,b]

History of Breast or Ovarian Cancer in the Family? If Yes, Complete Checklist		
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 same side of family		
Male breast cancer at any age in any relative		
Jewish ancestry		

[a] See Bellcross et al.[22]

[b] Referral if 2 or more checks in table.

Table 4. Pedigree Assessment Tool[a,b]

Risk Factor	Score for Every Family Member With Breast or Ovarian Cancer Diagnosis, Including Second-/Third-Degree Relatives
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
Total	

[a] See Hoskins et al,[23] Teller et al.[24]

[b] Score 8 or greater is the optimal referral threshold.

Scope of Review

To update its 2013 recommendation, the USPSTF commissioned a systematic review[28,40] on risk assessment, genetic counseling, and genetic testing for potentially harmful *BRCA1/2* mutations in

Table 5. Seven-Question Family History Screening[a,b]

No.	Questions
1	Did any of your first-degree relatives have breast *or* ovarian cancer?
2	Did any of your relatives have bilateral breast cancer?
3	Did any man in your family have breast cancer?
4	Did any woman in your family have breast *and* ovarian cancer?
5	Did any woman in your family have breast cancer before age 50 y?
6	Do you have 2 or more relatives with breast *and/or* ovarian cancer?
7	Do you have 2 or more relatives with breast *and/or* bowel cancer?

[a] See Ashton-Prolla et al,[25] Fischer et al.[26]

[b] One positive response initiates referral.

Table 6. International Breast Cancer Intervention Study Model[a,b]

No.	Risk Factor
1	Personal history: current age, age at menopause, age at menarche, childbirth history, menopausal status, use of menopausal hormone therapy
2	Personal breast history, breast density (optional), prior breast biopsy, history of cancer (breast or ovarian), genetic testing
3	Ashkenazi Jewish inheritance
4	Family history (genetic risk)—relatives with breast or ovarian cancer, age at diagnosis, genetic testing

[a] See Fischer et al,[26] Cuzick.[27]

[b] Referral for genetic testing if the personal risk level for a mutation in breast cancer susceptibility gene 1 or 2 is 10% or greater.

asymptomatic women who have never been diagnosed with *BRCA*-related cancer, as well as those with a previous breast, ovarian, tubal, or peritoneal cancer diagnosis who have completed treatment and are considered cancer free. The USPSTF reviewed interventions to reduce the risk for breast, ovarian, tubal, or peritoneal cancer in women with potentially harmful *BRCA1/2* mutations, including intensive cancer screening (eg, earlier and more frequent mammography or magnetic resonance imaging [MRI] of the breast), medications (eg, tamoxifen, raloxifene, or aromatase inhibitors), and risk-reducing surgery (eg, mastectomy or salpingo-oophorectomy). Although male breast cancer, pancreatic cancer, prostate cancer, and melanoma are associated with *BRCA1/2* mutations, discussion of these types of cancer is outside the scope of this recommendation.

Accuracy of Familial Risk Assessment

The USPSTF reviewed studies of familial risk stratification tools that could be used in primary care settings to determine the likelihood of potentially harmful *BRCA1/2* mutations. These tools are primarily intended for use by health care clinicians untrained in genetic cancer risk assessment to guide referral to genetic counselors for more definitive evaluation. In general, these tools elicit information about factors associated with increased likelihood of *BRCA1/2* mutations, including family and personal history of cancer (including types of cancer and age of diagnosis) and ancestry (Ashkenazi Jewish). Because risk assessment is primarily based on family history, it is unclear how women with an unknown family history should be assessed for *BRCA1/2* mutation risk.

Models that have been validated in studies include the Ontario Family History Assessment Tool (Table 1),[15-18] Manchester Scoring System (Table 2),[16-21,41] Referral Screening Tool (Table 3),[22] Pedigree Assessment Tool (Table 4),[23,24] 7-Question Family History Screening Tool (Table 5),[25] and the International Breast Cancer Intervention Study instrument (also known as Tyrer-Cuzick) (Table 6), and their variations.[26] The USPSTF found that these tools are clinically useful predictors of which individuals should be referred for genetic counseling. Compared with results of other models or genetic testing in studies, these tools all have sensitivity estimates between 77% and 100% and areas under the receiver operating characteristic curve between 0.68 and 0.96,[28] although some models have been evaluated in only 1 study.[22,25,26] The USPSTF reviewed a study of brief versions of BRCAPRO (eg, BRCAPRO-LYTE), designed for primary care clinicians, followed by the full BRCAPRO (used by genetic counselors) and found that the sequential testing scheme identified a similar number of *BRCA* mutation carriers as the full BRCAPRO.[42] The USPSTF recognizes that each risk assessment tool has advantages and limitations and found insufficient evidence to recommend one tool over another.

Effectiveness of Genetic Counseling, Genetic Testing, and Interventions

To understand the full benefits and harms of genetic counseling, the USPSTF reviewed studies on pretest and posttest counseling, *BRCA1/2* mutation testing, and interventions.

Pretest and Posttest Counseling

The USPSTF reviewed 28 studies on pretest counseling.[43-72] Studies reported measures of distress associated with genetic counseling for *BRCA*-related cancer, including cancer worry (17 studies), anxiety (13 studies), and depression (7 studies). In general, pretest genetic counseling either decreased or had no effect on breast cancer worry, anxiety, and depression.[28] Twenty-two studies examined understanding of risk, with most reporting either improved understanding (14 studies)[45,48,53,55-58,61,64,65,67-69,72,73] or no association (6 studies),[43,52,59,62,70,71] 1 study reporting decreased understanding,[60] and 1 study reporting mixed results.[46] Five studies that evaluated the effects of genetic counseling on *BRCA1/2* mutation testing intention found decreased intent to test in 4 studies[45,53,58,67] and increased intent in 1 study.[74]

Although several studies included discussion of management options as part of the pretest counseling process, none evaluated benefits or harms of counseling conducted after receiving test results.

BRCA1/2 Mutation Testing

One good-quality trial (n = 1034) of women and men of Ashkenazi Jewish ancestry evaluated population-based *BRCA1/2* mutation testing vs family history–based testing.[75] Results showed that a strategy of population-based testing for founder mutations detected more *BRCA1/2* mutation carriers than testing persons who met family history criteria. However, no clinical outcomes were reported and, because not all participants had *BRCA1/2* mutation testing, the accuracy of this strategy could not be determined. Genetic testing generally improved risk perception, with increased perceived risk of breast and ovarian cancer risk in *BRCA1/2* mutation carriers and decreased perceived risk in persons testing negative.[76,77]

Interventions

Studied interventions to reduce risk for cancer in women who are *BRCA1/2* mutation carriers include earlier, more frequent, or more intensive cancer screening (eg, breast MRI or mammography); use of risk-reducing medications (eg, selective estrogen receptor modulators or aromatase inhibitors); and risk-reducing surgery (eg, mastectomy or salpingo-oophorectomy).

The USPSTF reviewed 11 randomized clinical trials of selective estrogen receptor modulators and aromatase inhibitors, although none were conducted specifically in women who were *BRCA1/2* mutation carriers. Results of meta-analysis[78] indicated clinically significant reductions in invasive breast cancer with the use of tamoxifen, raloxifene, and aromatase inhibitors, with 7 fewer events per 1000 women for tamoxifen (4 trials),[79-82] 9 fewer events per 1000 women for raloxifene (2 trials),[83,84] and 16 fewer events per 1000 women for aromatase inhibitors (2 trials),[85-89] assuming 5 years of treatment. Tamoxifen reduced invasive breast cancer more than raloxifene in the head-to-head trial (relative risk, 1.24 [95% CI, 1.05-1.47]).[90] Risk reduction persisted at least 8 years after discontinuation in the 2 tamoxifen trials providing long-term follow-up data. All medications reduced estrogen receptor–positive, but not estrogen receptor–negative, invasive breast cancer. Breast cancer–specific and all-cause mortality were not reduced.[78]

In cohort studies of high-risk women and women who were *BRCA1/2* mutation carriers, risk-reducing surgery such as mastectomy (6 studies),[91-97] oophorectomy (7 studies),[98-104] or salpingo-oophorectomy (2 studies)[91,105] were associated with reduced risk for breast or ovarian cancer. Bilateral mastectomy was associated with a 90% to 100% reduced breast cancer incidence and 81% to 100% reduced breast cancer mortality. Oophorectomy was associated with 81% to 100% reduced ovarian cancer incidence. In general, there was no association between oophorectomy or salpingo-oophorectomy and reduced breast cancer risk, although some studies showed reduced risk in younger women (age <50 years).[78,98,99]

The USPSTF found no studies on the benefits of intensive screening for *BRCA*-related cancer on clinical outcomes in women who are *BRCA1/2* mutation carriers.

Harms of Genetic Counseling, Genetic Testing, and Interventions

The USPSTF reviewed the psychological effects of test results. Nine studies evaluated breast cancer worry or distress after genetic testing. Increased worry was found in 7 studies,[77,106-111] particularly in women who are *BRCA1/2* mutation carriers, and 2 studies reported decreased worry.[112,113] Studies reporting anxiety related to genetic testing were mixed, with 4 reporting increased anxiety,[106,109,113,114] 2 reporting decreased anxiety,[111,115] and 6 reporting no association.[75,108,112,116-118] Two studies noted higher anxiety in women who were not tested compared with those who were tested.[111,119] Of the 8 studies evaluating depression, none reported increases in anxiety after genetic testing.[75,108,111,112,115,117,118,120]

Intensive screening for breast and ovarian cancer is associated with false-positive results, additional imaging tests, and surgery for women without cancer. In a retrospective analysis of a cohort of women with potentially harmful *BRCA1/2* mutations or first-degree relatives with *BRCA1/2* mutations, women screened with mammography were more likely to have additional imaging tests than those screened with MRI.[121] In 2 studies comparing mammography with MRI for breast cancer screening in which 18% to 100% of study participants were *BRCA1/2* mutation carriers, MRI was associated with higher false-positive rates (14% vs 5.5% in the first round of screening; $P < .001$[122]; 15% vs 11% in another study[121]). Intensive screening for ovarian cancer using transvaginal ultrasound demonstrated high false-positive rates (3.4%).[123] A second study in women who were *BRCA1/2* mutation carriers reported a diagnostic surgery rate of 55% after annual screening with transvaginal ultrasound and serum tumor marker cancer antigen 125 measurements for women without cancer.[124] Most women did not experience anxiety after screening with MRI, mammography, or clinical breast examination, although women recalled for additional testing reported transient anxiety.[125]

Eight placebo-controlled trials and 1 head-to-head trial of tamoxifen and raloxifene reported harms of risk-reducing medications. Raloxifene and tamoxifen increased risk for thromboembolic events compared with placebo, and raloxifene caused fewer events than tamoxifen in the head-to-head trial.[78,126,127] An increased risk of endometrial cancer was seen with tamoxifen (4 cases per 1000 women) but not with raloxifene or aromatase inhibitors. Women using tamoxifen had more cataract procedures compared with placebo or raloxifene.[79,90] The most common adverse effects were vasomotor symptoms and vaginal discharge, itching, or dryness for tamoxifen and vasomotor symptoms and leg cramps for raloxifene.[28]

Thirteen studies of mastectomy[128-140] and 9 studies of oophorectomy or salpingo-oophorectomy[141-145] reported harms associated with surgical interventions, although most were small in size and had mixed outcomes. For mastectomy, complication rates ranged from 49% to 69%.[28] Complications included numbness, pain, tingling, infection, swelling, breast hardness, bleeding, organizing hematoma, failed reconstruction, breathing problems, thrombosis, and pulmonary embolism.[28] Postsurgical complications associated with oophorectomy/salpingo-oophorectomy included bleeding, pain, infection, and hematoma formation, with 1% to 3% of women in 1 study reporting such complications.[142] In another small study of women who were *BRCA1/2* mutation carriers, most women reported worsening vasomotor symptoms and decreased sexual function.[146] Seven studies reported psychological outcomes in women receiving risk-reducing mastectomy[132-140] and 3 studies in those receiving risk-reducing oophorectomy/salpingo-oophorectomy.[143-145] Commonly reported symptoms included reductions in body image, sexual activity/satisfaction, and general mental health (anxiety/depression symptoms); however, many of these symptoms were transient.[28]

Estimate of Magnitude of Net Benefit

For women whose family or personal history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are moderate. For women whose family history is not associated with an increased risk for harmful mutations in the *BRCA1/2* genes, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are small to none.

The USPSTF found adequate evidence that the overall harms of risk assessment, genetic counseling, genetic testing, and interventions are small to moderate.

For women whose family history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes, the USPSTF concludes with moderate certainty that the net benefit outweighs the harm of risk assessment and referral to genetic counseling for consideration of testing, detection, and intervention is moderate. For women whose family history is not associated with an increased risk for harmful mutations in the *BRCA1/2* genes, the USPSTF concludes with moderate certainty that the harms of risk assessment and referral to genetic counseling for consideration of testing, detection, and intervention outweigh the benefits.

How Does the Evidence Fit With Biological Understanding?

The *BRCA1* and *BRCA2* genes are tumor suppressor genes. Harmful 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 *BRCA1/2* mutations. Genetic testing may identify these mutations. Several options are available to reduce cancer risk in patients found to be mutation carriers.

Response to Public Comment

A draft version of this Recommendation Statement was posted for public comment on the USPSTF website from February 19 through March 18, 2019. In response to public comments, the USPSTF clarified language regarding risk assessment and included additional information on the risk assessment tools referenced in the recommendation. It also incorporated language clarifying that the recommendation includes women with a personal history of *BRCA*-related cancer who have completed treatment and are considered cured.

Comments requested that the population under consideration be expanded to include other *BRCA*-associated cancers such as pancreatic cancer, melanoma, and prostate cancer, as well as men with breast or prostate cancer. The USPSTF recognizes the association of *BRCA1/2* mutations with cancers such as pancreatic, prostate, and melanoma. However, the scope of the recommendation is limited to the prevention of breast, ovarian, tubal, and peritoneal cancer because the net benefit demonstrated was in the prevention of these cancers. The USPSTF did not review evidence on the benefits or harms of risk assessment, genetic counseling, and genetic testing in men.

Several comments requested changes to the recommendation related to newer genetic testing options. This includes the use of multigene panels, expanding the recommendation to include other gene mutations linked to increased risk of cancer (eg, *TP53, ATM, PALB2*), and the use of direct-to-consumer testing. The USPSTF acknowledges that there is increasing access to multigene panels; however, the clinical significance of identifying pathogenic variants in multigene panels requires further investigation. The evidence is currently limited on other moderate penetrance genes, given their relatively low incidence in the population. The USPSTF's recommendation focuses on *BRCA1/2* mutations because they are more prevalent and the findings are clinically actionable. The USPSTF found no evidence on the benefits or harms associated with the use of direct-to-consumer testing. Current National Comprehensive Cancer Network guidelines recommend that multigene testing be offered in the context of professional genetic expertise for pretest and posttest.[29] The USPSTF added language emphasizing that the net benefit relies on genetic counseling to accompany testing results, including results from direct-to-consumer testing.

Update of Previous USPSTF Recommendation

In 2005 and 2013, the USPSTF recommended that women whose family history is associated with an increased risk for potentially harmful mutations in the *BRCA1/2* genes be referred for genetic counseling and evaluation for *BRCA1/2* testing. It also recommended against routine referral for genetic counseling or routine *BRCA1/2* mutation testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1/2* genes.[14,147] This Recommendation Statement is consistent with the USPSTF's previous recommendation.

Since 2013, the validity of genetic testing for *BRCA1/2* mutations has been established and the potential benefits and harms of previously reviewed interventions, such as risk-reducing medications and surgery, have been studied for longer follow-up periods. In addition, there have been more studies of newer imaging techniques (breast MRI), surgical procedures (salpingo-oophorectomy rather than oophorectomy alone), and medications (aromatase inhibitors). The updated recommendation expands the population eligible for screening to include women with a previous breast, ovarian, tubal, or peritoneal cancer diagnosis who have completed treatment and are considered cancer free and more explicitly includes ancestry associated with *BRCA1/2* mutations (ie, founder mutations) as a risk factor.

Recommendations of Others

The National Comprehensive Cancer Network provides specific criteria for genetic counseling and testing.[29] The American College of Medical Genetics and the American Society of Clinical Oncology recommend testing for *BRCA1/2* mutations only when an individual has personal or family cancer history suggestive of inherited cancer susceptibility, the test can be adequately interpreted, and the results will aid in management.[148,149] The American College of Obstetricians and Gynecologists recommends performing a hereditary cancer risk assessment and subsequent referral to a specialist in cancer genetics if necessary.[150] The Society for Gynecologic Oncology recommends that individuals with a likelihood of inherited predisposition to cancer based on personal or family history should be offered genetic counseling.[151] The American Society of Breast Surgeons recommends that genetic testing be made available to all patients with a personal history of breast cancer.[152] The National Institute for Health and Care Excellence recommends that health care professionals respond to a patient who presents with concerns but should not, in most instances, actively seek to identify persons with a family history of breast cancer.[153] It recommends that in some circumstances, including when a patient has concerns about relatives with breast cancer, a first- and second-degree family history be taken in primary care to assess risk. Referral to secondary care is recommended if risk factors are identified in family history taking.[153] The European Society for Medical Oncology follows the recommendations of the National Institute for Health and Care Excellence for initial risk assessment and the decision when to perform genetic counseling and testing.[154]

ARTICLE INFORMATION

Correction: This article was corrected on October 11, 2019, for incorrect information in an author affiliation and on November 12, 2019, for an incorrect word that affected the meaning of a sentence.

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