JAMA | US Preventive Services Task Force | EVIDENCE REPORT

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

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Pathogenic mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2* increase risks for breast, ovarian, fallopian tube, and peritoneal cancer in women; interventions reduce risk in mutation carriers.

OBJECTIVE To update the 2013 US Preventive Services Task Force review on benefits and harms of risk assessment, genetic counseling, and genetic testing for *BRCA1/2*-related cancer in women.

DATA SOURCES Cochrane libraries; MEDLINE, PsycINFO, EMBASE (January 1, 2013, to March 6, 2019, for updates; January 1, 1994, to March 6, 2019, for new key questions and populations); reference lists.

STUDY SELECTION Discriminatory accuracy studies, randomized clinical trials (RCTs), and observational studies of women without recently diagnosed *BRCA1/2*-related cancer.

DATA EXTRACTION AND SYNTHESIS Data on study methods, setting, population characteristics, eligibility criteria, interventions, numbers enrolled and lost to follow-up, outcome ascertainment, and results were abstracted. Two reviewers independently assessed study quality.

MAIN OUTCOMES AND MEASURES Cancer incidence and mortality; discriminatory accuracy of risk assessment tools for *BRCA1/2* mutations; benefits and harms of risk assessment, genetic counseling, genetic testing, and risk-reducing interventions.

RESULTS For this review, 103 studies (110 articles; N = 92 712) were included. No studies evaluated the effectiveness of risk assessment, genetic counseling, and genetic testing in reducing incidence and mortality of *BRCA1/2*-related cancer. Fourteen studies (n = 43 813) of 8 risk assessment tools to guide referrals to genetic counseling demonstrated moderate to high accuracy (area under the receiver operating characteristic curve, 0.68-0.96). Twenty-eight studies (n = 8060) indicated that genetic counseling was associated with reduced breast cancer worry, anxiety, and depression; increased understanding of risk; and decreased intention for testing. Twenty studies (n = 4322) showed that breast cancer worry and anxiety were higher after testing for women with positive results and lower for others; understanding of risk was higher after testing. In 8 RCTs (n = 54 651), tamoxifen (relative risk [RR], 0.69 [95% CI, 0.59-0.84]; 4 trials), raloxifene (RR, 0.44 [95% CI, 0.24-0.80]; 2 trials), and aromatase inhibitors (RR, 0.45 [95% CI, 0.26-0.70]; 2 trials) were associated with lower risks of invasive breast cancer compared with placebo; results were not specific to mutation carriers. Mastectomy was associated with 90% to 100% reduction in breast cancer incidence (6 studies; n = 2546) and 81% to 100% reduction in breast cancer mortality (1 study; n = 639); oophorectomy was associated with 69% to 100% reduction in ovarian cancer (2 studies; n = 2108); complications were common with mastectomy.

CONCLUSIONS AND RELEVANCE Among women without recently diagnosed *BRCA1/2*-related cancer, the benefits and harms of risk assessment, genetic counseling, and genetic testing to reduce cancer incidence and mortality have not been directly evaluated by current research.

JAMA. 2019;322(7):666-685. doi:10.1001/jama.2019.8430

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Pathogenic mutations in the breast cancer susceptibility genes *BRCA1* and *BRCA2* are associated with increased risks for breast, ovarian, fallopian tube, and peritoneal cancer in women, breast cancer in men, and, to a lesser degree, pancreatic and early-onset prostate cancer[1-6]; *BRCA2* is also associated with melanoma.[3,4] *BRCA1/2* mutations cluster in families, exhibiting an autosomal dominant pattern of transmission in either the maternal or paternal lineage. Penetrance, the probability of developing cancer in *BRCA1/2* mutation carriers, is variable, and many carriers never develop cancer.

BRCA1/2 mutations occur in 1 in 300 to 500 individuals in the general population[7-10] and account for 5% to 10% of breast and 15% of ovarian cancer.[7,11] Specific *BRCA1/2* mutations, known as founder mutations, are clustered among certain groups, such as Ashkenazi Jews,[12-14] among others. In general, breast cancer risk increases to 45% to 65% by age 70 years for pathogenic mutations in either the *BRCA1* or the *BRCA2* gene[15,16]; ovarian, fallopian tube, or peritoneal cancer risk increases to 39% for mutations in *BRCA1* and 10% to 17% in *BRCA2*.[15-23] Genetic counseling involves identifying and advising individuals at risk for inherited cancer susceptibility and is recommended before and after *BRCA1/2* mutation testing.[24-26] Accreditation standards outline essential training and skills for genetics professionals.[27] Interventions to reduce risk for cancer in mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications; and risk-reducing surgery, including mastectomy and salpingo-oophorectomy.

This report was used by the US Preventive Services Task Force (USPSTF) to update the 2013 recommendation on risk assessment, genetic counseling, and genetic testing for *BRCA1/2*-related cancer in women with clinically relevant family cancer histories (B recommendation) but not for women without family histories (D recommendation).[28,29] This report focuses on *BRCA1/2* mutations because they are more prevalent and penetrant than other types,[4,30-32] estimates of associated cancer risk are available, and interventions to reduce risk for carriers have been studied.[32-34]

Methods

Scope of Review

Detailed methods are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing1.[35] **Figure 1** shows the analytic framework and key questions (KQs) that guided this review. Studies of male breast cancer, pancreatic cancer, prostate cancer, and melanoma are outside the scope of this review, although all types of cancer are considered during familial risk assessment. Ovarian, fallopian tube, and peritoneal carcinomas are overlapping epithelial malignancies in which the designation of the 3 primary sites is often arbitrary. For the purpose of this review, the 3 disease sites are collectively referred to as ovarian carcinoma. The screening population was expanded for this update to include women with unknown mutation status and either no previous diagnosis of *BRCA1/2*-related cancer or previous diagnosis but completion of cancer treatment.

Data Sources and Searches

The Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, Ovid EMBASE, and MEDLINE (January 1, 2013, to March 6, 2019, for updates; January 1, 1994, to March 6, 2019, for new KQs and populations) were searched for relevant English-language articles (eMethods 1 in the Supplement); reference lists were manually reviewed. Studies published before 2013 were identified from prior systematic reviews for the USPSTF.[29,37]

Study Selection

Investigators reviewed abstracts and full-text articles using prespecified eligibility criteria (eTable 1 in the Supplement).[35,36] A second reviewer independently confirmed results of the initial review, and discrepancies were resolved by consensus with a third reviewer if needed.

Randomized clinical trials (RCTs), systematic reviews, prospective and retrospective cohort studies, case-control studies, and diagnostic accuracy evaluations that addressed KQs were eligible. These included studies of the accuracy of risk assessment tools (KQ2a), outcomes of genetic counseling and testing (KQ1, KQ2b, KQ2c, KQ2d), and effectiveness studies of interventions to reduce risk of *BRCA1/2*-related cancer among mutation carriers (KQ4). Interventions included intensive screening (earlier and more frequent mammography, breast magnetic resonance imaging [MRI], transvaginal ultrasound [TVUS], cancer antigen 125 [CA-125] levels), risk-reducing medications (tamoxifen, raloxifene, aromatase inhibitors), and risk-reducing surgery (mastectomy, salpingo-oophorectomy). Risk assessment tools were included only if they were intended for use by nonspecialists in genetics to guide referrals, such as the Pedigree Assessment Tool (PAT), and were applicable to US clinical settings. Evaluation of complex models used in genetic counseling was outside the scope of this review. Studies of any design were included to describe potential harms of risk assessment, genetic counseling, genetic testing, and risk-reducing interventions (KQ3, KQ5).

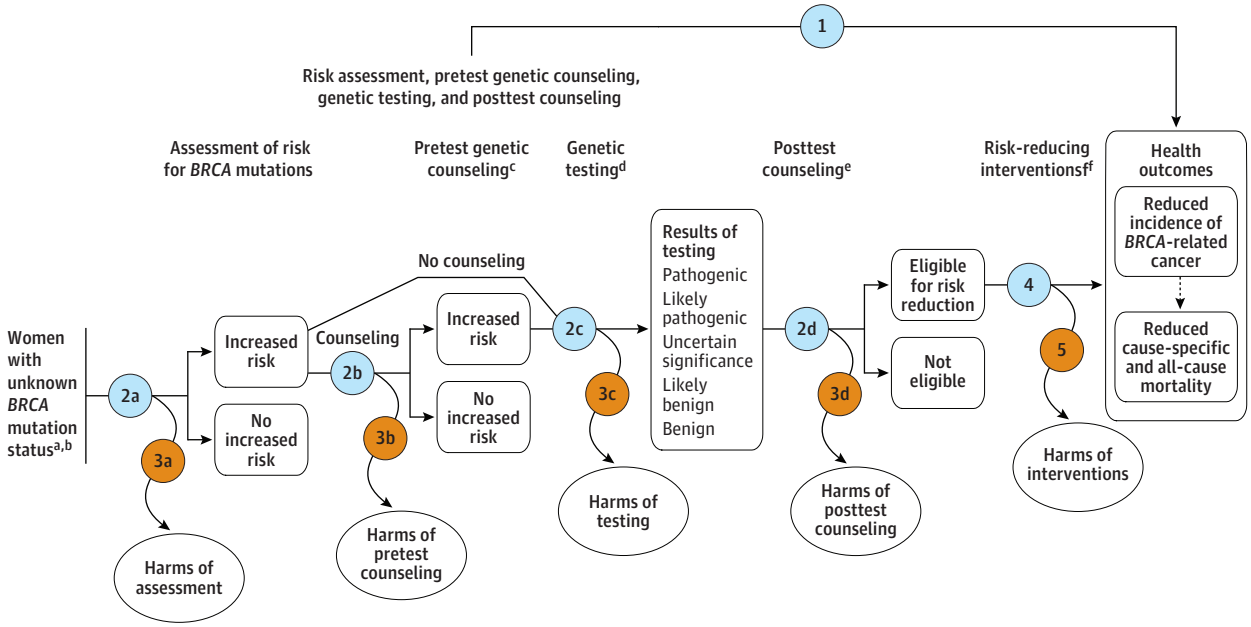
Studies that included women with histories of breast or ovarian cancer were excluded from the 2013 review. For this update, studies that included women who were diagnosed with breast or ovarian cancer at least 5 years before enrollment and completed cancer treatment were included to ensure that genetic testing was intended for risk reduction rather than treatment purposes. Studies that did not report the time since breast or ovarian cancer diagnosis were excluded.

Data Extraction and Quality Assessment

For the included RCTs and observational studies, investigators abstracted data on study design; setting; population characteristics (including age, ethnicity, and diagnosis); eligibility criteria; interventions; numbers enrolled and lost to follow-up; method of outcome ascertainment; and results for each outcome. For studies of risk assessment tools, investigators abstracted data on study design; population characteristics; eligibility criteria; reference standards; risk factors included in the models; and performance measures of the models. A second investigator reviewed accuracy of abstracted data.

Two investigators independently applied criteria developed by the USPSTF[36] to rate the quality of each study as good, fair, or poor (eMethods 2 and eTables in the Supplement). Discrepancies were resolved through a consensus process.

Figure 1. Analytic Framework: Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer in Women



Key questions

1 In women with unknown *BRCA1/2* mutation status, does risk assessment, genetic counseling, and genetic testing result in reduced incidence of *BRCA1/2*-related cancer and cause-specific and all-cause mortality?

2
a. What is the accuracy of familial risk assessment for *BRCA1/2*-related cancer when performed by a nonspecialist in genetics in a clinical setting? What are the optimal ages and intervals for risk assessment?

b. What are the benefits of pretest genetic counseling in determining eligibility for genetic testing for *BRCA1/2*-related cancer? (Includes improved accuracy of risk assessment and pretest probability for testing and improved patient knowledge, understanding of benefits and harms of interventions to reduce risk, risk perception, satisfaction, and health and psychological outcomes.)

c. What are optimal testing approaches to determine the presence of pathogenic *BRCA1/2* mutations in women at increased risk for *BRCA1/2*-related cancer? (Includes testing other high-risk family members, including men, before testing the index patient and using specific types of tests or multigene panels.)

d. What are optimal posttest counseling approaches to interpret results and determine eligibility for interventions to reduce risk of *BRCA1/2*-related cancer? (Includes improved patient knowledge, understanding of benefits and harms of interventions to reduce risk, risk perception, satisfaction, and health and psychological outcomes.)

3 What are adverse effects of

a. Risk assessment

b. Pretest genetic counseling

c. Genetic testing

d. Posttest counseling for *BRCA1/2*-related cancer?

(Includes inaccurate risk assessment; inappropriate testing; false-positive and false-negative results; adverse effects on the patient's family relationships; overdiagnosis and overtreatment; false reassurance; incomplete testing; misinterpretation of test results; anxiety; cancer worry; and ethical, legal, and social implications.)

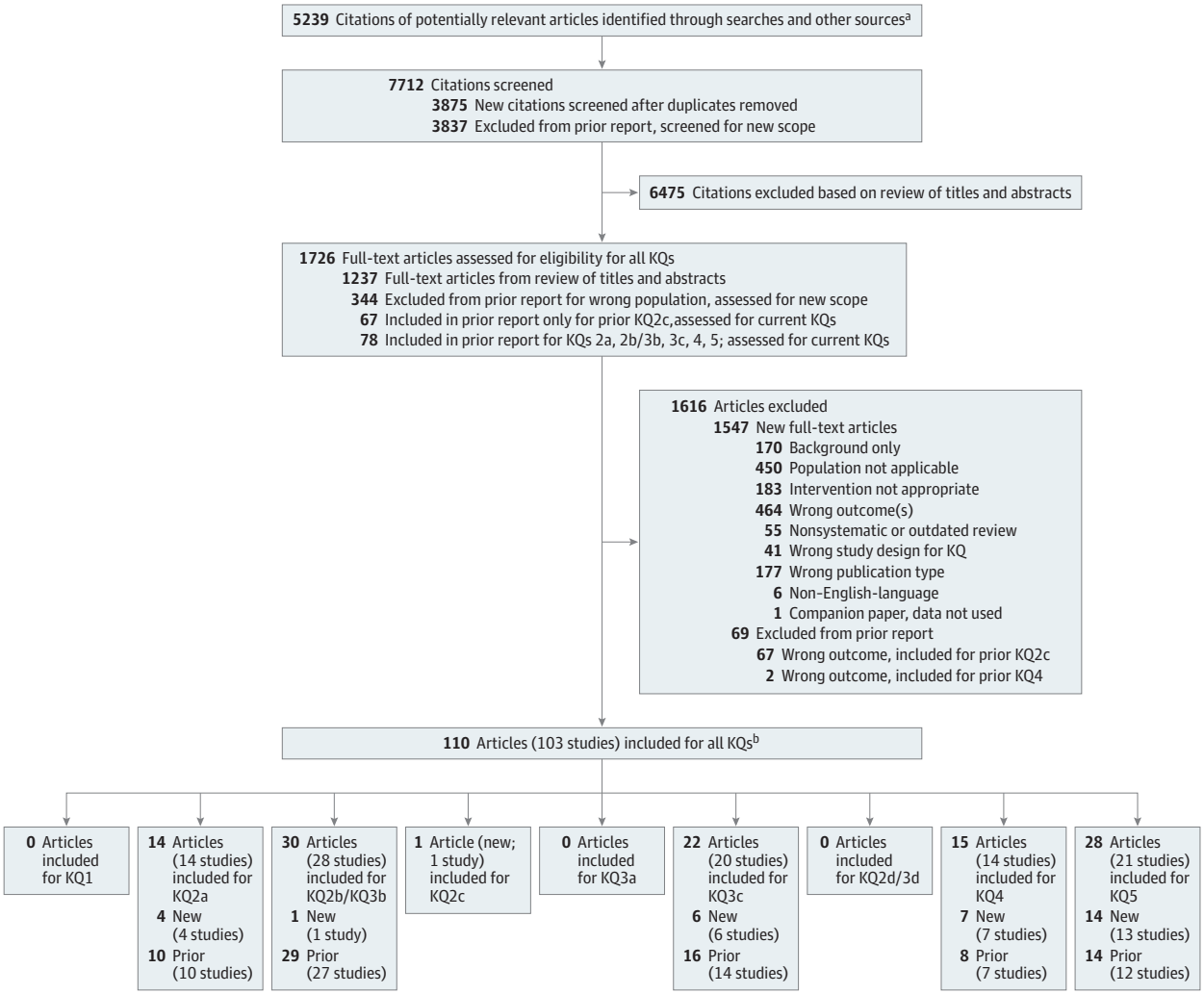
4 Do interventions reduce the incidence of *BRCA1/2*-related cancer and mortality in women at increased risk? (Includes intensive screening [earlier and more frequent screening; use of additional screening methods], use of risk-reducing medications [aromatase inhibitors; tamoxifen; raloxifene], and risk-reducing surgery [mastectomy; salpingo-oophorectomy; other procedures] when performed for prevention purposes.)

5 What are adverse effects of interventions to reduce risk for *BRCA1/2*-related cancer? (Includes immediate and long-term harms associated with screening, risk-reducing medications, and risk-reducing surgery and ethical, legal, and social implications.)

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display key questions addressed by the review to allow the USPSTF to evaluate the effectiveness and harms of a preventive service. The questions are depicted by linkages that relate interventions to outcomes; a dashed line indicates a linkage that is known and not addressed by the evidence review. Refer to the USPSTF procedure manual for further details.[36] *BRCA* indicates breast cancer susceptibility gene.

[a] Clinically significant pathogenic mutations in the *BRCA1* and *BRCA2* genes associated with increased risk for breast cancer, ovarian cancer, or both. [b]Includes women who may have a previous diagnosis of breast or ovarian cancer but have completed treatment and are considered cancer-free. [c]Descriptions of genetic counseling, scope of services, and appropriate clinicians are described in the full report. [d]Testing may be conducted on the index patient, her relative with cancer, or her relative with highest risk, as appropriate. [e]Includes interpretation of results, determination of eligibility for risk-reducing interventions, and patient decision-making. [f]Interventions include early detection through intensive screening, use of risk-reducing medications, and risk-reducing surgery when performed for prevention purposes.

Figure 2. Literature Search Flow Diagram: Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer in Women



BRCA indicates breast cancer susceptibility gene; KQ, key question.

[a] Includes reference lists of relevant articles, studies, and systematic reviews; suggestions from reviewers.

[b] One hundred three studies in 110 publications provided data; some addressed more than 1 KQ.

Data Synthesis and Analysis

For all KQs, the overall quality of evidence was rated good, fair, or poor based on study quality, consistency of results, precision of estimates, study limitations, risk of reporting bias, and applicability, and summarized in a table.[36] No statistical meta-analysis was performed.

Results

For this review, 103 studies (110 articles; N = 92 712) were included (**Figure 2**)[38-147]: 14 discriminatory accuracy studies (n = 43 813), 15 RCTs (n = 4132), 59 cohort studies (n = 41 300), 2 case-control studies (n = 481), 12 before-and-after studies (n = 1372), and 1 systematic review (n = 1614).

Effectiveness of Risk Assessment, Genetic Counseling, and Genetic Testing in Reducing Incidence and Mortality of *BRCA1/2*-Related Cancer

Key Question 1. In women with unknown *BRCA1/2* mutation status, does risk assessment, genetic counseling, and genetic testing result in reduced incidence of *BRCA1/2*-related cancer and cause-specific and all-cause mortality?

No studies were identified for KQ1.

Accuracy of Risk Assessment and Pretest Genetic Counseling

Key Question 2a. What is the accuracy of familial risk assessment for *BRCA1/2*-related cancer when performed by a nonspecialist in genetics in a clinical setting? What are the optimal ages and intervals for risk assessment?

Fourteen discriminatory accuracy studies (n = 43 813) of 8 risk assessment tools met inclusion criteria (**Table 1**),[38-51] including 4 new studies that evaluated existing tools.[42,44,47,51] No studies evaluated optimal ages and intervals for risk assessment. Most studies used results of *BRCA1/2* mutation testing as the reference standard, although 2 studies used clinical criteria that involved risk estimates from more complex risk assessment models.[39,41]

Risk assessment tools were developed to predict the likelihood of *BRCA1/2* mutations in individuals and generally include variations of familial risk factors. These include *BRCA1/2* mutations previously detected in relatives; Ashkenazi Jewish ancestry; numbers, ages, and types of relatives affected with breast or ovarian cancer; and presentations of cancer that are highly suggestive of *BRCA1/2* mutations, such as male or bilateral breast cancer, breast and ovarian cancer in the same person, and young age (<50 years) at cancer onset. Risk assessment tools included initial and revised versions of the Ontario Family History Assessment Tool (FHAT), 7-question Family History Screening (FHS-7), Manchester Scoring System (MSS), PAT, Referral Screening Tool (RST), International Breast Cancer Intervention Study (IBIS) risk model, and brief versions of BRCAPRO, a complex statistical model typically used by genetic counselors.

Results of the 4 new studies[42,44,47,51] were consistent with the 10 previous studies[38-41,43,45,46,48-50] indicating moderate to high diagnostic accuracy of risk assessment tools in predicting *BRCA1/2* mutations in individuals (area under the receiver operating characteristic curve [AUC], 0.68-0.96). A new study of a revised version of the MSS that integrated pathology data of the family member diagnosed with cancer[47] reported a higher AUC than the previous version[43,45,50,51] (0.80 [95% CI, 0.78-0.82] for revised MSS vs 0.77 [95% CI, 0.75-0.79] for previous MSS). In new validation studies, the discriminatory accuracy of referral tools was comparable to that of more complex tools for the PAT (AUC, 0.71 for PAT; 0.68 for Myriad II; 0.72 for Penn II)[51] and IBIS (AUC, 0.75 [95% CI, 0.74-0.76] for IBIS; 0.79 [95% CI, 0.78-0.80] for the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm [BOADICEA]; 0.80 [95% CI, 0.78-0.81] for BRCAPRO; 0.75 [95% CI, 0.73-0.76] for eClaus).[44] In another new study, the accuracy of 3 brief versions of BRCAPRO followed by the full BRCAPRO if indicated was similar to using BRCAPRO alone (AUC, 0.78-0.79 for brief versions followed by full BRCAPRO; AUC, 0.78 [95% CI, 0.76-0.81] for full BRCAPRO alone).[42]

Key Question 2b. What are the benefits of pretest genetic counseling in determining eligibility for genetic testing for *BRCA1/2*-related cancer?

Twenty-eight studies (30 articles; n = 8060) were included (**Table 2**),[52-81] including 1 new before-and-after study.[52] The new study showed that agreement between a woman's understanding of her breast cancer risk and her genetic counselor's appraisal decreased 1 year after counseling compared with immediately after (49% agreement vs 35%) among 89 women in the Netherlands.[52]

Studies included in the previous review reported additional outcomes. Of 17 studies evaluating breast cancer worry, 1 reported increased measures after genetic counseling but only in women at high risk[60]; 8 reported decreases[54,57,61,62,65,67,69,76]; and 8 reported no associations.[56,58,63,68,71,72,80,81] Some studies showed mixed results that varied by subgroup or type of counseling.[55,60,61,71]

Thirteen studies evaluated anxiety associated with genetic counseling; none reported increases, 5 reported decreases,[58,60,62,77,78] and 8 reported no associations.[54,64,68,69,73,76,80,81] Seven studies of depression also showed no increases in measures of depression, while 1 study indicated decreases[78] and 6 reported no associations.[54,58,64,73,76,80]

Of 22 studies evaluating the association of genetic counseling with women's understanding of their cancer risk, 14 reported increased understanding,[57,58,60,62,63,65-68,72,74,77,78,80] 1 reported decreased understanding,[70] 6 (including the new study) reported no associations,[52,56,69,73,75,81] and 1 reported mixed results.[64] Five studies evaluated the association of genetic counseling with intention for genetic testing; 1 study reported increased intention,[71] 4 reported decreased intention,[57,60,63,67] and none reported no associations.

BRCA1/2 Mutation Testing and Posttest Genetic Counseling

Key Question 2c. What are optimal testing approaches to determine the presence of pathogenic *BRCA1/2* mutations in women at increased risk for *BRCA1/2*-related cancer?

A new good-quality RCT randomized 691 women and 343 men of Ashkenazi Jewish ancestry (4 grandparents) to population-based *BRCA1/2* mutation testing vs family history–based testing in the United Kingdom.[96] The detected prevalence of *BRCA1/2* mutations among participants was 2.45% overall, with 13 *BRCA1/2* carriers identified by population testing and 9 by family history. Over 3 years of follow-up, 210 of the 438 family history–negative participants opted to complete testing that identified an additional 5 carriers among family history–negative participants.[96] Health outcomes related to increased detection, such as cancer incidence, mortality, and potential harms, were not determined. Short-term measures of anxiety, health anxiety, depression, distress, uncertainty, and quality of life were similar between testing groups.

Key Question 2d. What are optimal posttest counseling approaches to interpret results and determine eligibility for interventions to reduce risk of *BRCA1/2*-related cancer?

No studies were identified that specifically addressed posttest counseling.

Harms of Risk Assessment and Pretest Genetic Counseling

Key Question 3a. What are adverse effects of risk assessment?

No studies were identified for KQ3a.

Key Question 3b. What are adverse effects of pretest genetic counseling?

Twenty-eight studies (30 articles; n = 8060) of pretest genetic counseling included for KQ2b (Table 2)[52-81] were also included for KQ3b because the outcome measures were designed to indicate benefits or harms. Results indicated that counseling was not associated with increased breast cancer worry, anxiety, or depression as described above. Two studies indicated women have less understanding of their risks after genetic counseling,[64,70] while 14 studies indicated increased understanding.[57,58,60,62,63,65-68,72,74,77,78,80]

Key Question 3c. What are adverse effects of genetic testing?

Twenty observational studies (22 articles; n = 4322), including 6 new studies[82,89,93,95,96,102] and 14 (in 16 articles) from the 2013 review,[83-88,90-92,94,97-101,103] met inclusion criteria (eTable 2 in the Supplement).[82-95,97-104] Studies determined psychological effects of genetic testing for *BRCA1/2*-related cancer, measured as changes in worry, anxiety, depression, and understanding of risk. Two studies

Table 1. Risk Assessment Tools to Predict Individual Risk for *BRCA1/2* Mutations in Primary Care Settings (Key Question 2a)[a]

Model	Data Collection and Calculation	Population (No.)	Relatives With Breast or Ovarian Cancer	Other Factors	Comparison With Other Models	Reference Standard	Performance Characteristics for Predicting Risk for *BRCA1/2* Mutations	Quality Rating
BRCAPRO-LYTE BRCAPRO-LYTE-plus BRCAPRO-LYTE-simple[42]	Evaluates brief versions of BRCAPRO[b] to guide referral to genetic counseling that uses full BRCAPRO	Patients with personal or family cancer history in 3 US hospital databases (4057)	First- and second-degree	No. and types of relatives with breast and ovarian cancer; ages diagnosed	BRCAPRO	Mutation testing	Estimates based on different cutpoints: BRCAPRO-LYTE: sensitivity, 57%-93%; specificity, 10%-56% BRCAPRO-LYTE-plus: sensitivity, 39%-76%; specificity, 40%-83% BRCAPRO-LYTE-simple: sensitivity, 43%-83%; specificity, 29%-79%	Fair
Seven-question Family History Screening[39]	One positive response to 7 items is referral threshold	Women visiting primary care clinics in Brazil (9218 completed FHS-7, 1246 referred, 902 completed evaluation)	First-degree	Any relatives with breast cancer aged ≤50 y; bilateral breast cancer; breast and ovarian cancer in same person; male breast cancer; ≥2 relatives with breast or ovarian cancer; ≥2 relatives with breast or colon cancer	None	Criteria for hereditary breast cancer syndrome[c]	Sensitivity, 88% (95% CI, 83%-91%) Specificity, 56% (95% CI, 54%-59%) PPV, 24% (95% CI, 21%-27%) NPV, 97% (95% CI, 95%-98%) AUC, 0.83 (95% CI, 0.81-0.85)	Good
International Breast Cancer Intervention Study Model[38,44,49]	Compares performance with other established models	German Hereditary Breast and Ovarian Cancer Consortium (7352 families); families in cancer genetics clinics in the United Kindom (1889) and Canada (300)	Female first- and second-degree relatives, affected cousins, and half-sisters	Environmental factors for female index patients only	BOADICEA BRCAPRO eClaus Manchester Penn II Myriad II FHAT	Mutation testing	German study: sensitivity, 77%; specificity, 56.5% PPV, 36%; NPV, 88.5% AUC, 0.75 (95% CI, 0.74-0.76) UK study: AUC, 0.74 (95% CI, 0.71-0.77) Canadian study: AUC, 0.47 (95% CI, 0.28-0.69)	Fair to good
Manchester scoring system[38,40,43,48,49]	Assigns points for responses to 12 items; referral threshold ≥10 points per mutation or ≥15 collectively (≥10% mutation probability)	Developed in families with cancer history in the United Kingdom (422); evaluated in 4 additional studies in United Kingdom and Canada (2880)	First-, second-, and third-degree	Type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, and age at diagnosis	BOADICEA BRCAPRO FHAT Myriad II	Mutation testing	Estimates based on different evaluation studies (≥10% mutation probability): sensitivity, 58%-93%; specificity, 33%-71%; AUC, 0.75-0.80	Fair to good
Modified Manchester scoring system[47]	Assigns points for responses; referral threshold ≥10 points per mutation or ≥15 collectively (≥10% mutation probability)	German Hereditary Breast and Ovarian Cancer Consortium (9390 families)	First-, second-, and third-degree	New version includes pathology (histology and hormone receptor status) of index patient in addition to original factors: type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, age at diagnosis	Original MSS (MSS-2004) without pathology; MSS-2009 with pathology; recalibrated MSS (MSS-recal) with pathology	Mutation testing	≥10% Mutation probability: MSS-2004: AUC, 0.77 (95% CI, 0.75-0.79) MSS-2009: AUC, 0.80 (95% CI, 0.78-0.82) MSS-recal: AUC, 0.82 (95% CI, 0.80-0.83)	Fair

(continued)

Table 1. Risk Assessment Tools to Predict Individual Risk for *BRCA1/2* Mutations in Primary Care Settings (Key Question 2a)[a] (continued)

Model	Data Collection and Calculation	Population (No.)	Relatives With Breast or Ovarian Cancer	Other Factors	Comparison With Other Models	Reference Standard	Performance Characteristics for Predicting Risk for *BRCA1/2* Mutations	Quality Rating
Ontario Family History Assessment Tool[45,48-50]	Assigns points for responses to 17 items; referral threshold ≥10 (≥22% lifetime risk for breast or ovarian cancer)	Developed in families with cancer history in Canada (184); evaluated in 3 additional studies in Canada and United States (3566)	First-, second-, and third-degree	Age at diagnosis; bilateral breast cancer; breast and ovarian cancer in same person; male breast cancer; colon and prostate cancer	Claus BRCAPRO	Mutation testing	Estimates based on different evaluation studies (≥22 lifetime risk): sensitivity, 91%-94%; specificity, 15%-51% PPV, 31% AUC, 0.68-0.83	Fair to good
Pedigree Assessment Tool[46,51]	Assigns points for responses to 5 items; referral threshold ≥8 points (≥10% mutation probability)	Developed in women without breast cancer presenting for screening mammography at a US community hospital (3906); evaluated in families in United States (520 families)	First-, second-, and third-degree	Breast cancer age ≤50 or >50 y; ovarian cancer at any age; male breast cancer; Ashkenazi Jewish ancestry	Myriad II Penn II	Mutation testing Myriad II	Mutation testing as reference standard (≥10% mutation probability): sensitivity, 95.9%; specificity, 20.1% PPV, 0.32; NPV, 0.93 AUC, 0.71 Myriad II as reference standard (≥10% mutation probability): sensitivity, 100%; specificity, 93% PPV, 0.63; NPV, 1.00 AUC, 0.96	Fair
Referral Screening Tool[41]	≥2 Positive responses to 13 items is referral threshold (≥10% mutation probability)	Unselected women undergoing screening mammogram (2464 completed screening tool, 296 randomly evaluated)	First- and second-degree	Breast cancer at age ≤50 y (self or relatives); ovarian cancer at any age (self or relatives); ≥2 relatives aged >50 y with breast cancer on same side of family; male breast cancer; Jewish ancestry	None	Pedigree analysis and estimates of mutation risk based on models (BOADICEA; BRCAPRO; FHAT; Myriad II)[d]	≥10% Mutation probability: sensitivity, 81%; specificity, 92% PPV, 0.80; NPV, 0.92 AUC, 0.87	Good

Abbreviations: AUC, area under the receiver operating characteristic curve; BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; FHAT, Family History Assessment Tool; MSS, Manchester Scoring System; NPV, negative predictive value; PPV, positive predictive value.

[a] Individual clinical scoring instruments are detailed in Appendix C1 and quality ratings in Appendix B1 of the full report.[35]

[b] BRCAPRO-LYTE applies the BRCAPRO model using only information on the numbers and types of first- and second-degree relatives, which relatives are affected with breast and ovarian cancer, and their ages of diagnosis; BRCAPRO-LYTE-plus does not collect data on ages of affected relatives but imputes ages based on a large external data set; BRCAPRO-LYTE-simple imputes the number of relatives for each type of cancer and ages of unaffected relatives.

[c] Based on evaluation including pedigree analysis, lifetime risk estimates from established models (Claus; Gail; Tyrer-Cuzick; Penn II), American Society of Clinical Oncology criteria, and review by 2 clinical geneticists.

[d] Detailed 4-generation cancer pedigrees analyzed using 4 established hereditary risk models (BRCAPRO, Myriad II, BOADICEA, FHAT), with a 10% or greater *BRCA1/2* mutation probability or FHAT score of 10 or greater as the definition of "high risk."

Table 2. Studies of Benefits and Harms of Pretest Genetic Counseling (Key Questions 2b, 3b)[a]

			Breast Cancer Worry		Anxiety		Depression		Accuracy of Risk Perception		Intent to Participate in Testing		
Source	No.	Clinician	Increase	Decrease	Increase	Decrease	Increase	Decrease	More	Less	Increase	Decrease	Quality Rating
Albada et al,[52] 2016	89	Geneticist, genetic counselor								–			NA
Bennett et al,[54] 2008	128	Genetic counselor	–	+	–	–	–	–					NA
Bennett et al,[55] 2009	128	Genetic counselor	–										NA
Bloom et al.,[56] 2006	163	Genetic counselor	–	–					–	–			Poor
Bowen et al,[59] 2002	354[b]	Genetic counselor									–	+	Fair
Bowen et al,[58] 2004	354[b]	Genetic counselor	–	–	–	+	–	–	+	–			Fair
Bowen et al,[57] 2006	221	Psychologist, genetic counselor	–	+					+	–	–	+	Fair
Brain et al,[60] 2002	740[b]	Geneticist, nurse	–	+	–	+			+	–			Good
Brain et al,[61] 2011	263[b]	Physician	–	+									NA
Braithwaite et al,[62] 2005	72	Nurse	–	+	–	+			+	–			Fair
Burke et al,[63] 2000	356	Genetic counselor	–	–					+	–		+	Fair
Cull et al,[64] 1998	144	Geneticist, physician			–	–	–	–	+	+			Good
Fry et al,[65] 2003	263	Geneticist, physician, nurse	–	+					+	–			Fair
Gurmankin et al,[66] 2005	125	Physician							+	–			NA
Helmes et al,[67] 2006	340	Genetic counselor	–	+					+	–	–	+	Fair
Hopwood et al,[68] 1998	174	Genetic counselor	–	–	–	–			+	–			Fair
Hopwood et al,[69] 2004	256	Genetic counselor	–	+	–	–			–	–			NA
Kelly et al,[70] 2008	78	Genetic counselor							–	+			NA
Lerman et al,[72] 1996	227	Genetic counselor	–	–					+	–			Fair
Lerman et al,[71] 1999	364	Nurse, genetic counselor	–	–							+	–	Fair
Lobb et al,[73] 2004	193	Geneticist, genetic counselor, physician			–	–	–	–	–	–			Good
Matloff et al, [74]2006	64	Genetic counselor							+	–			Fair
Mikkelsen et al,[75] 2007	1971[b]	Physician							–	–			Fair
Mikkelsen et al,[76] 2009	1971[b]	Physician	–	+	–	–	–	–					Fair
Pieterse et al,[77] 2011	77	Geneticist, genetic counselor			–	+			+	–			NA
Roshanai et al,[78] 2009	163	Nurse			–	+	–	+	+	–			Fair
Watson et al,[80] 1998	115	Geneticist	–	–	–	–	–	–	+	–			Good
Watson et al,[81] 1999	283	Geneticist	–	–	–	–			–	–			Good

Abbreviation: NA, not applicable.

[a] Plus (+) indicates statistically significant relationship with genetic counseling; minus (–) indicates studied, but no statistically significant relationship with genetic counseling; empty cell indicates not studied.

[b] Uses the same population in more than 1 study.

were not included in the 2013 review because they enrolled women previously treated for breast or ovarian cancer.[82,102]

Studies included cohort, case-control, and before-and-after designs that were small; lacked comparison groups; varied in methodology, enrollment criteria, and outcomes; and had high loss to follow-up. Results indicate that breast cancer worry and anxiety generally increased for women with positive results and decreased for others, although measures varied across studies. Understanding of risk improved after receiving test results.

Key Question 3d. What are adverse effects of posttest genetic counseling?

No studies were identified that specifically addressed posttest counseling.

Effectiveness and Harms of Interventions to Reduce *BRCA1/2*-Related Cancer and Mortality in *BRCA1/2* Mutation Carriers

Key Question 4. Do interventions reduce the incidence of *BRCA1/2*-related cancer and mortality in women at increased risk?

No effectiveness trials of intensive screening for breast or ovarian cancer in *BRCA1/2* mutation carriers that report cancer or mortality outcomes have been published. Studies of performance characteristics of intensive screening may be useful in clinical decision-making, but these studies do not directly address this key question. In 2 studies including 1364 *BRCA1/2* mutation carriers, sensitivity of screening for breast cancer was 63% to 69% for MRI, 25% to 62% for mammography, and 66% to 70% for combined modalities; specificity was 91% or higher for either modality alone or combined (eTable 3 in the Supplement).[148,149] In a study of 459 *BRCA1/2* mutation carriers, sensitivity of screening for ovarian cancer was 43% for TVUS, 71% for CA-125, and 71% for combined modalities; specificity was 99% for either modality alone or combined.[132]

No trials of risk-reducing medications reported results specifically for *BRCA1/2* mutation carriers. A systematic review and meta-analysis[150] of 8 placebo-controlled RCTs (n = 54 651) of tamoxifen,[151-154] raloxifene,[155,156] and the aromatase inhibitors anastrozole[157-159] and exemestane[160,161] and a head-to-head trial of tamoxifen vs raloxifene (n = 19 747)[162] provide efficacy outcomes for women at various risk levels. Trials were clinically heterogeneous and data were not available to compare doses, duration, and timing of use. Tamoxifen (risk ratio [RR], 0.69 [95% CI, 0.59-0.84]; 4 trials; n = 28 421), raloxifene (RR, 0.44 [95% CI, 0.24-0.80]; 2 trials; n = 17 806), and aromatase inhibitors (RR, 0.45 [95% CI, 0.26- 0.70]; 2 trials; n = 8424) were associated with lower risk of invasive breast cancer after 3 to 5 years of use compared with placebo (eTable 4 in the Supplement); tamoxifen had a greater effect than raloxifene in the head-to-head trial (RR, 1.24 [95% CI, 1.05-1.47]; n = 19 747).[162] Risks for invasive breast cancer were lower in all subgroups evaluated based on family history of breast cancer. Reduction was significant for estrogen receptor (ER)–positive, but not ER-negative, breast cancer, noninvasive breast cancer, and mortality.

Six observational studies (7 articles; n = 2546) of risk-reducing mastectomy,[105-110,118] 2 of risk-reducing salpingo-oophorectomy (n = 2379),[105,111] and 7 of oophorectomy alone (n = 6807)[112-117,119] were included (**Table 3**). Risk-reducing bilateral mastectomy was associated with 90% to 100% reduction in breast cancer incidence for high-risk women and *BRCA1/2* mutation carriers.[105-110] Breast cancer–specific mortality was lower by 81% to 100% after risk-reducing mastectomy in 1 study of 639 women.[108]

Newer studies of oophorectomy or salpingo-oophorectomy that control for biases did not show associations between surgery and breast cancer risk,[111,112,114] although some studies showed reduced risk specifically among younger women after surgery.[112-115] Oophorectomy was associated with 69% to 100% reduction in ovarian cancer risk among 2108 women in 2 studies[105,113,116] but with no differences in cancer-specific mortality.[105]

Key Question 5. What are adverse effects of interventions to reduce risk for *BRCA1/2*-related cancer?

For breast cancer screening, 3 studies (4 articles; n = 2631) of false-positive and false-negative results, recall rates, and diagnostic procedures[136-139] and 3 studies (4 articles; n = 513) of discomfort, pain, breast cancer worry, anxiety, and depression[128,143-145] were included (eTable 5 in the Supplement). In these studies, false-positive rates,[137] recall,[138] additional imaging,[136] and benign biopsy results[136] were higher with MRI than with mammography. In most studies, women experienced no anxiety or depression after screening with MRI, mammography, or clinical breast examination, and breast cancer worry decreased over time.[128,143-145] For ovarian cancer screening, studies indicated a false-positive rate of 3.4% (55/1595) for TVUS[123] and a diagnostic surgery rate of 55% (6/11), with benign results for combined TVUS and CA-125.[133]

No studies evaluated the adverse effects of risk-reducing medications specifically in *BRCA1/2* mutation carriers, although adverse effects were reported in 9 RCTs of women at various levels of risk,[150] including placebo-controlled trials of tamoxifen,[151-154] raloxifene,[155,156] and the aromatase inhibitors anastrozole[157-159] and exemestane[160,161] and a head-to-head RCT of tamoxifen vs raloxifene.[162] Data on long-term effects were incomplete, particularly for aromatase inhibitors. Tamoxifen (RR, 1.93 [95% CI, 1.33-2.68]; 4 trials; n = 28 421) and raloxifene (RR, 1.56 [95% CI, 1.11-2.60]; 2 trials; n = 17 806) were associated with increased thromboembolic events compared with placebo (eTable 6 in the Supplement),[150] and numbers of events were higher for tamoxifen than for raloxifene in the head-to-head trial (RR, 0.75 [95% CI, 0.60-0.93]; n = 19 747).[162] Tamoxifen was also associated with increased endometrial cancer (RR, 2.25 [95% CI, 1.17-4.41]; 3 trials; n = 11 721)[150] and cataracts.[151] All medications were associated with undesirable adverse effects for some women, such as vasomotor and musculoskeletal symptoms.

Twelve observational studies (13 articles; n = 2684), including 8 new studies (n = 750), of surgical complications, physical symptoms, or psychological outcomes related to risk-reducing mastectomy[120,121,124,125,127,130-132,134,140,142,146,147] and 5 studies (n = 530), including 4 new studies (n = 449), related to risk-reducing salpingo-oophorectomy or oophorectomy[122,126,129,135,141] were included (eTable 7 in the Supplement). In studies of mastectomy, 50% or more of women experienced surgical complications including necrosis, pain, infection, hematoma, and implant problems.[121,130-132,140,142] While body image and psychological symptoms worsened after surgery for some women, most measures returned to baseline later.[127,131,134,146] Rates of surgical complications with salpingo-oophorectomy were approximately 4% (7/159) in a single study,[135] although women had worsening of vasomotor symptoms, sexual functioning, and fatigue.[129,141]

Table 3. Studies of Risk-Reducing Surgery (Key Question 4)

Source	Inclusion Criteria	No. With *BRCA1/2* Mutation	Mean Age at Surgery, y	Cancer Incidence		Mortality	Mean Follow-up, y	Quality Rating
				Breast	Ovarian			
Mastectomy vs Surveillance								
Flippo-Morton et al,[107] 2016	*BRCA1/2* carrier; with or without breast or ovarian cancer	123 *BRCA1* 122 *BRCA2* 1 *BRCA1* + *BRCA2*	At testing: >35: 51/87 ≤35: 36/87	0/38 vs 5/36	NR	NR	2.5	Fair
Heemskerk-Gerritsen et al,[110] 2013	*BRCA1/2* carrier; no history of cancer	405 *BRCA1*; 165 *BRCA2*	35 (median)	Person-years: 0/1379 vs 57/2017	NR	All-cause person-years: 6/2253 vs 1/1384; HR, 0.20 (95% CI, 0.02-1.68) Breast cancer person-years: 4/2253 vs 1/1384; HR, 0.29 (95% CI, 0.03-2.61)	8.5 vs 6.3 (median)	Fair
Skytte et al,[118] 2011	*BRCA1/2* carrier	201 *BRCA1* 10 *BRCA2*	NR	3/96 vs 16/211; HR, 0.39 (95% CI, 0.12-1.36)	NR	NR	NR	Good
Domchek et al,[105] 2010	*BRCA1* carrier	415 *BRCA1*	37	0/43 vs 19/372	NR	NR	2.7	Fair
		245 *BRCA2*	39	0/32 vs 15/213			2.5	
Evans et al,[106] 2009	Lifetime risk of breast cancer >25%	High-risk; 202 *BRCA1/2*	NR	Observed vs expected: 307 vs 21.3	NR	NR	7.5	NA
Hartmann et al,[109] 2001 Hartmann et al,[108] 1999	Family history of breast cancer	214 High-risk	42	Observed vs expected: 3/214 vs 37; risk reduction, 92% (95% CI, 77%-98%)	2	Observed vs expected: 2/214 vs 10; risk reduction, 81% (95% CI, 31%-98%)	14 (median)	NA
		425 Moderate-risk	42	Observed vs expected: 4/425 vs 37; risk reduction, 89.5% ($P < .001$)	0	Observed vs expected: 0/425 vs 10; risk reduction, 100% (95% CI, 70%-100%)	14 (median)	
		18 *BRCA1* or *BRCA2*	41	Observed vs expected: 0/18 vs 6.1/18; risk reduction, 100% (95% CI, 51%-100%)	NR	NR	13.4 (median)	
Salpingo-oophorectomy or Oophorectomy vs Surveillance								
Kotsopoulos et al,[112] 2016	*BRCA1/2*; no cancer	2969 *BRCA1* 725 *BRCA2*	46.2 (surgery) 33.4 (no surgery at baseline)	Annual incidence, all women: 1.87% vs 1.59%; HR, 0.89 (95% CI, 0.69-1.14) All ages: *BRCA1*: HR, 0.97 (0.73-1.29); *BRCA2*: HR, 0.68 (95% CI, 0.38-1.21) Age <50 y: *BRCA1*: HR, 0.84 (0.58-1.21); *BRCA2*: HR, 0.17 (95% CI, 0.05-0.61)	NR	NR	5.6	Fair

(continued)

Table 3. Studies of Risk-Reducing Surgery (Key Question 4) (continued)

Source	Inclusion Criteria	No. With *BRCA1/2* Mutation	Mean Age at Surgery, y	Cancer Incidence		Mortality	Mean Follow-up, y	Quality Rating
				Breast	Ovarian			
HEBON Heemskerk-Gerritsen et al,[111] 2015	*BRCA1/2*; no cancer	589 *BRCA1*; 233 *BRCA2*	44 (surgery) 33 (no surgery)	All: 42/346 vs 47/476; HR, 1.09 (95% CI, 0.67-1.77) *BRCA1*: HR, 1.21 (95% CI, 0.72-2.06) *BRCA2*: HR, 0.54 (95% CI, 0.17-1.66) Age <51 y: HR, 1.11 (95% CI, 0.65-1.90) Age ≥51 y, HR, 1.78 (95% CI, 0.52-6.15)	NR	NR	3.2 (median)	Fair
EMBRACE Mavaddat et al,[114] 2013	*BRCA1/2*; no cancer or history of unilateral breast cancer	501 *BRCA1* 485 *BRCA2*	41.2 at enrollment	18/309 vs 46/679; HR, 0.62 (95% CI, 0.35-1.09) *BRCA1*: HR, 0.52 (95% CI, 0.24-1.13) *BRCA2*: HR, 0.79 (95% CI, 0.35-1.80) Age <45 y: HR, 0.39 (95% CI, 0.17-0.87) Age ≥45 y: HR, 1.14 (95% CI, 0.50-2.61)	NR	NR	3.3	Fair
Domchek et al,[105] 2010	*BRCA1* carrier	1003 *BRCA1*	42	32/236 vs 129/633; HR, 0.63 (95% CI, 0.41-0.96)	6/342 vs 49/661; HR, 0.31 (95% CI, 0.12-0.82)	All-cause: 8/327 vs 43/608; HR, 0.52 (95% CI, 0.24-1.14)	5.6	Fair
		554 *BRCA2*	46	7/100 vs 94/401; HR, 0.36 (95% CI, 0.16-0.82)	0/123 vs 14/431	All-cause: 0/120 vs 17/403	5.8	
Shah et al,[117] 2009	*BRCA1/2* carriers or mutation probability >75%	51 *BRCA1* 41 *BRCA2*	47 at enrollment (median)	Any oophorectomy: 9/80 vs 2/13 Age ≤40 y: 3/25 vs 8/68	NR	NR	3.2 (median)	Fair
Kramer et al,[113] 2005	*BRCA1*-positive family; no bilateral mastectomy	98 *BRCA1*-positive	NR	6/33 vs 27/65; HR, 0.38 (95% CI, 0.15-0.97)	NR	NR	16.5	Fair
		353 *BRCA1*-negative		1/34 vs 4/319				
		222 Unknown mutation status		0/18 vs 5/204				

(continued)

Table 3. Studies of Risk-Reducing Surgery (Key Question 4) (continued)

Source	Inclusion Criteria	No. With *BRCA1/2* Mutation	Mean Age at Surgery, y	Cancer Incidence		Mortality	Mean Follow-up, y	Quality Rating
				Breast	Ovarian			
Rebbeck et al,[116] 2002	*BRCA1/2;* no ovarian cancer or unilateral oophorectomy; no history of breast cancer or mastectomy	*459 BRCA1* *94 BRCA2*	42.0 (surgery) 40.9 (no surgery)	21/99 vs 60/142; HR, 0.47 (95% CI, 0.29-0.77) Age <35 y: HR, 0.39 (95% CI, 0.15-1.04) Age 35-50 y: HR, 0.49 (95% CI, 0.26-0.90) Age ≥50 y: HR, 0.52 (95% CI, 0.10-2.70)	2/259 vs 58/292; HR, 0.04 (95% CI, 0.01-0.16) No history of breast cancer: HR, 0.06 (95% CI, 0.01-0.25) Age 35-50 y: HR, 0.03 (95% CI, 0.01-0.20) Age ≥50 y: HR, 0.11 (95% CI, 0.02-0.76)	NR	8.2 vs 8.8	Fair
Olson et al,[115] 2004	Women with bilateral oophorectomy	55 High-risk	<60	Observed vs expected: 3/55 vs 5.4; RR, 0.56 (95% CI, 0.1-1.33)	NR	NR	NA	NA
		41 High-risk	<50	Observed vs expected: 1/41 vs 3.9; RR, 0.26 (95% CI, 0.01-0.99)				
		193 Moderate-risk	<60	Observed vs expected: 9/193 vs 10.9; RR, 0.83 (95% CI, 0.38-1.44)				
		130 Moderate-risk	<50	Observed vs expected: 5/130 vs 7.7; RR, 0.65 (95% CI, 0.21-1.32)				
Struewing et al,[119]1995	Families with ≥3 cases of ovarian cancer or ≥2 cases ovarian cancer and ≥1 case breast cancer before age 50 y	390 (12 families) first-degree relatives of individuals with breast or ovarian cancer	NR	3/44 vs 14/346	2/44 vs 8/346	NR	NR	Poor

Abbreviations: *BRCA*, breast cancer susceptibility gene; EMBRACE, Epidemiological Study of Familial Breast Cancer; HEBON, Hereditary Breast and Ovarian Cancer Research Group Netherlands; HR, hazard ratio; NA, not applicable; NR, not reported; RR, relative risk.

Table 4. Summary of Evidence

Populations or Interventions	Studies; Observations (No.); Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1: Benefits of Risk Assessment, Genetic Counseling, and Genetic Testing						
Risk assessment; genetic counseling; genetic testing	No studies	NA	NA	NA	Insufficient	NA
KQ2a: Accuracy of Familial Risk Assessment Tools By Nonspecialists						
Risk assessment for *BRCA1/2*-related cancer risk	14 Discriminatory accuracy studies of 8 risk assessment tools (n = 43 813)	Tools have moderate to good discriminatory accuracy in predicting the probability of familial *BRCA1/2*-related cancer risk in individuals (AUC, 0.68-0.96)	Consistent; precise	While some studies enrolled small numbers or inadequately described methods, most studies met criteria for fair and good quality	Moderate for benefit	Moderate to high
KQ2a: Optimal Ages and Intervals for Risk Assessment						
Risk assessment for *BRCA1/2*-related cancer risk	No studies	NA	NA	NA	Insufficient	NA
KQ2b: Benefits of Pretest Genetic Counseling						
Pretest genetic counseling	28 Studies (1 systematic review; 14 RCTs; and 4 cohort, 1 case-control, and 8 before-and-after) (n = 8060)	Genetic counseling decreases cancer worry, anxiety, and depression; increases the accuracy of risk perception; and decreases intention for mutation testing Face-to-face counseling preferred in some studies	Consistent; precise	Dissimilar comparison groups; small sizes; dissimilar interventions; heterogeneous outcome measures	High for benefit	High
KQ2c: Optimal Testing Approaches						
BRCA1/2 mutation testing	1 RCT (n = 1034)	Universal testing of Ashkenazi Jews for founder mutations detected more *BRCA1/2* carriers than testing only those meeting family history criteria	NA	All participants had genetic counseling, so not a true population approach; not all were tested, so cannot determine accuracy of strategy	Low for benefit	Moderate
KQ2d: Optimal Posttest Counseling Approaches						
Posttest genetic counseling	No studies	NA	NA	NA	Insufficient	NA
KQ3a: Harms of Risk Assessment						
Risk assessment for *BRCA1/2*-related cancer risk	No studies	NA	NA	NA	Insufficient	NA
KQ3b: Harms of Pretest Genetic Counseling						
Pretest genetic counseling	28 Studies (1 systematic review; 14 RCTs; and 4 cohort, 1 case-control, and 8 before-and-after) (n = 8060)	Genetic counseling did not cause adverse effects in studies but decreased cancer worry, anxiety, and depression; increased the accuracy of risk perception; and decreased intention for mutation testing	Consistent; precise	Dissimilar comparison groups; small sizes; dissimilar interventions; heterogeneous outcome measures	Moderate for harms	Moderate
KQ3c: Harms of Genetic Testing						
BRCA1/2 mutation testing	20 Studies (1 RCT, 13 cohort, 1 case-control, 4 before-and-after, and 1 case series) (n = 4322)	Breast cancer worry and anxiety increase for women with positive results and decrease for others, while risk perception improves	Consistent; precise	Lack of studies with comparison groups; variations in methodology and enrollment criteria; heterogeneous outcome measures; high loss to follow-up	Moderate for benefits and harms (varies by test result)	Moderate
KQ3d: Harms of Posttest Counseling						
Posttest genetic counseling	No studies	NA	NA	Not applicable	Insufficient	NA

(continued)

Discussion

This evidence report reviewed current research on benefits and harms of risk assessment, genetic counseling, and genetic testing for *BRCA1/2*-related cancer in women. **Table 4** summarizes the evidence reviewed.

This review expands the scope of previous reports for the USPSTF[29,37] by including studies of untested women with previous diagnoses of *BRCA1/2*-related cancer who completed treatment

Table 4. Summary of Evidence (continued)

Populations or Interventions	Studies; Observations (No.); Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ4: Interventions to Reduce *BRCA1/2*-Related Cancer and Mortality						
Intensive screening	No effectiveness trials; 6 studies of test characteristics of screening (n = 5087)	Breast MRI has higher sensitivity than mammography for screening *BRCA1/2* carriers (71% vs 41%); specificity is comparable (90% vs 95%) Sensitivity of screening for ovarian cancer, 43% for TVUS and 71% for CA-125; specificity, 99% for either	NA	Descriptive studies that do not provide data on effectiveness	Insufficient	NA
Risk-reducing medications (tamoxifen, raloxifene, aromatase inhibitors [anastrozole; exemestane])	No trials for *BRCA1/2* carriers; 9 RCTs for general populations (n = 74 170)	Tamoxifen, raloxifene, anastrozole, and exemestane reduced invasive breast cancer and ER+ breast cancer compared with placebo No differences for ER− or noninvasive breast cancer, all-cause or breast cancer-specific mortality	Consistent; precise	No results for *BRCA1/2* carriers specifically; clinical heterogeneity across trials from varying eligibility criteria, adherence, and ascertainment of certain outcomes	Insufficient for *BRCA1/2* carriers specifically; high for benefit for general populations	High for general populations
Risk-reducing surgery	6 Observational studies of mastectomy; 7 observational studies of oophorectomy (n = 9938)	Bilateral mastectomy reduced breast cancer incidence 90%-100% and breast cancer mortality 81%-100% for high-risk women and mutation carriers Oophorectomy or salpingo-oophorectomy reduced breast cancer 37%-83% in some instances; salpingo-oophorectomy reduced ovarian cancer 69%-100%	Consistent; precise	Lack of studies with comparison groups; variations in methodology and enrollment criteria; heterogeneous outcome measures	Moderate for benefit	High
KQ5: Harms of Interventions to Reduce *BRCA1/2*-Related Cancer and Mortality						
Intensive screening	9 Observational studies (n = 5628)	For breast cancer screening, false-positive rates, additional imaging, and benign surgical procedures were higher for intensive screening using MRI vs mammography; benign diagnostic surgery rate of 55% for mutation carriers screened with TVUS and CA-125	Consistent; precise	Lack of studies with comparison groups; variations in methodology and enrollment criteria; heterogeneous outcome measures	Low for harm	High
Risk-reducing medications (tamoxifen, raloxifene, aromatase inhibitors [anastrozole; exemestane])	No trials for *BRCA1/2* carriers; 9 RCTs for general populations (n = 74 170)	Tamoxifen and raloxifene increased thromboembolic events and tamoxifen increased endometrial cancer and cataracts compared with placebo; no differences for DVT, PE, CHD events, or stroke	Consistent; precise	No results for *BRCA1/2* carriers specifically; clinical heterogeneity across trials from varying eligibility criteria, adherence, and ascertainment of certain outcomes	Insufficient for *BRCA1/2* carriers specifically; high for harm for general populations	High for general populations
Risk-reducing surgery	10 Observational studies of mastectomy; 4 observational studies of oophorectomy (n = 3073)	Harms include physical complications of surgery, postsurgical symptoms, and changes in body image; psychological symptoms generally improve over time, and some women have improved anxiety	Incon-sistent, imprecise	Lack of studies with comparison groups; variations in methodology and enrollment criteria; heterogeneous outcome measures	Low for harm	Moderate

Abbreviations: AUC, area under the receiver operator characteristic curve; *BRCA*, breast cancer susceptibility gene; CA-125, cancer antigen 125; CHD, coronary heart disease; DVT, deep vein thrombosis; ER+, estrogen receptor–positive; ER−, estrogen receptor–negative; KQ, key question; MRI, magnetic resonance imaging; NA, not applicable; PE, pulmonary embolism; RCT, randomized clinical trial; TVUS, transvaginal ultrasound.

and are considered cancer-free. These women may have missed earlier opportunities for risk assessment, genetic counseling, genetic testing, and risk-reducing interventions because these services may not have been available previously. Despite a comprehensive literature search, only 2 relevant studies that included this population were identified for this review, and they provided very limited information addressing key questions.

Four new studies evaluated the discriminatory accuracy of existing risk-assessment tools intended to guide referrals from primary care settings to genetic counseling. Studies indicated moderate to high predictive accuracy of revised versions of the MSS and brief versions of BRCAPRO and additional validation of the PAT and IBIS.

An RCT was the only study addressing a new KQ (KQ2c) regarding optimal testing approaches to determine the presence of pathogenic *BRCA1/2* mutations in women at increased risk for *BRCA1/2*-related cancer. Results indicated that population-based testing of Ashkenazi Jews detected more *BRCA1/2* mutations than family history–based testing. The study also found that potential harms, such as anxiety, depression, distress, uncertainty, and quality of life, were similar between groups. However, that study did not evaluate clinical outcomes central to decisions about screening, such as reduction in cancer incidence and mortality.

Only 1 new small study evaluated the benefits and harms of genetic counseling and indicated no association between a woman's understanding of her breast cancer risk and the genetic counselor's assessment, contrary to most studies that show improved understanding. Six new studies of benefits and harms of genetic testing were generally consistent with previous studies showing that breast cancer worry and anxiety increased after testing for those with positive results and decreased for others.

Two new RCTs of aromatase inhibitors indicated reductions in invasive breast cancer compared with placebo, although results were not specifically reported in *BRCA1/2* mutation carriers. Similar to tamoxifen and raloxifene, aromatase inhibitors were associated with reduced ER-positive but not ER-negative breast cancer, noninvasive breast cancer, or breast cancer–specific or all-cause mortality. Unlike tamoxifen and raloxifene, adverse effects of aromatase inhibitors in risk reduction trials are unclear because of short follow-up times. All medications were associated with symptomatic adverse effects, such as vasomotor and musculoskeletal symptoms.

New observational studies are consistent with previous studies showing that risk-reducing mastectomy was associated with reduced breast cancer and breast cancer mortality. Risk-reducing salpingo-oophorectomy was associated with reduced ovarian cancer incidence.

Despite the inclusion of 103 studies in this report, current research is limited or lacking for most KQs. Risk assessment, genetic counseling, and genetic testing to reduce *BRCA1/2*-related cancer incidence and mortality as a prevention service for women has not been directly addressed by current research that focuses on specific issues in highly selected populations. To determine the appropriateness of risk assessment and genetic testing for *BRCA1/2* mutations as a preventive service in primary care, more information is needed about mutation prevalence and the effect of testing in the general population. Research has focused on highly selected women in referral centers and generally reported short-term outcomes. Issues such as access to genetic testing and follow-up, effectiveness of screening approaches including risk stratification and multigene panels, effects of direct-to-consumer marketing, use of system supports, and patient acceptance and education require additional study.

Identification of appropriate candidates for genetic testing is essential to effective *BRCA1/2* mutation testing. Who should perform risk assessment and genetic counseling services, necessary skills, how it should be done, effectiveness of different methods to deliver services, and its effect on patient choices and outcomes are unresolved questions. Trials comparing types of clinicians and protocols could address these issues. What happens after patients are identified as high-risk in clinical settings is also not known. The consequences of genetic testing on individuals and their relatives need to be further understood. Well-designed investigations using standardized measures and enrolling participants that reflect the general population, including minority women, are needed. Additional research on effective interventions is also needed. Without effectiveness trials of intensive screening, practice standards have preceded supporting evidence. This information could improve patient decision-making and lead to better health outcomes.

Current research to identify women with pathogenic *BRCA1/2* mutations indicates that familial risk tools for primary care settings that evaluate individual risks can accurately guide referrals for genetic counseling. Comprehensive evaluations by genetic counselors provide estimates of individual risks for *BRCA1/2* mutations and identify candidates for genetic testing. Genetic counseling reduces breast cancer worry, anxiety, and depression; increases women's understanding of risk; and reduces intention for inappropriate mutation testing. Results of genetic testing improve a woman's understanding of her risk of developing *BRCA1/2*-related cancer depending on the type of mutation and specific test results.

Once a pathogenic mutation is identified, how to choose the best options for clinical management is currently unclear. Subjecting otherwise healthy women to clinical interventions requires careful consideration of benefits and harms. Although intensive screening for breast and ovarian cancer in *BRCA1/2* mutation carriers using MRI, TVUS, and CA-125 is supported by experts, its effectiveness in reducing cancer incidence and mortality has not been evaluated. Use of risk-reducing medications in mutation carriers has also not been studied. Tamoxifen and raloxifene increase thromboembolic events, tamoxifen increases endometrial cancer and cataracts, and all medications cause symptomatic adverse effects. While risk-reducing mastectomy and salpingo-oophorectomy are associated with reduced breast and ovarian cancer in *BRCA1/2* mutation carriers, they are invasive procedures with potential complications.

The process of familial risk assessment in primary care, referral and evaluation by genetic counselors, genetic testing, and use of intensive screening and risk-reducing medications and surgical procedures is complex. Each step of the pathway requires careful interpretation of information, consideration of future risks, and shared decision-making before moving on to the next step. Services must be well integrated and highly individualized to optimize benefits and minimize harms for patients as well as their families. Several evidence gaps relevant to prevention remain, and additional studies are necessary to fill them.

Limitations

This review has several limitations. First, it included only English-language articles and studies applicable to the United States, although this focus improves its relevance to the USPSTF recommendation. Second, the number, quality, and applicability of studies evaluated

in the evidence review varied widely. Third, most studies in this review included highly selected samples of women, some with preexisting breast or ovarian cancer or from high-risk groups that were defined in various ways, or from previously identified cancer kindreds. It is not known how the results of studies based on highly selected women in research settings, particularly in non-US settings, translate to general screening populations in US clinical practice.

Conclusions

Among women without recently diagnosed *BRCA1/2*-related cancer, the benefits and harms of risk assessment, genetic counseling, and genetic testing to reduce cancer incidence and mortality have not been directly evaluated by current research.

ARTICLE INFORMATION

Accepted for Publication: May 29, 2019.

Author Contributions: Dr Nelson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Nelson, Cantor, Haney.
Acquisition, analysis, or interpretation of data: Nelson, Pappas, Cantor, Haney, Holmes.
Drafting of the manuscript: Nelson, Pappas, Haney, Holmes.
Critical revision of the manuscript for important intellectual content: Nelson, Cantor, Holmes.
Obtained funding: Nelson.
Administrative, technical, or material support: Pappas, Cantor, Holmes.
Supervision: Nelson.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was funded under contract HHSA290201500009I, Task Order 7, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the US Preventive Services Task Force (USPSTF).

Role of the Funder/Sponsor: Investigators worked with the USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We gratefully acknowledge the following individuals for their contributions to this project: AHRQ Medical Officer Justin Mills, MD, and Pacific Northwest Evidence-based Practice Center expert consultant Elizabeth Swisher, MD, research librarian Andrew Hamilton, MLS, MS, and research assistant Lucy Stillman, BS. We also acknowledge past and current USPSTF members who contributed to topic deliberations. USPSTF members, external reviewers, and federal partner reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of this evidence report underwent external peer review from 5 federal partners at the Centers for Disease Control and Prevention, National Institutes of Health, and National Cancer Institute and 3 content experts (Mary Daly, MD, Risk Assessment Program, Department of Clinical Genetics, Fox Chase Cancer Center, Temple University; Kelly Metcalfe, PhD, University of Toronto and Familial Breast Cancer Research Institute at the Women's College Research Institute, Toronto, Onatario, Canada; and Robert Pilarski, MS, Clinical Cancer Genetics Program, Division of Human Genetics, The Ohio State University). Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying the USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

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