

# Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendation

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**Background:** Mutations in breast cancer susceptibility genes (*BRCA1* and *BRCA2*) are associated with increased risks for breast, ovarian, and other types of cancer.

**Purpose:** To review new evidence on the benefits and harms of risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women.

**Data Sources:** MEDLINE and PsycINFO between 2004 and 30 July 2013, the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews from 2004 through the second quarter of 2013, Health Technology Assessment during the fourth quarter of 2012, Scopus, and reference lists.

**Study Selection:** English-language studies about accuracy of risk assessment and benefits and harms of genetic counseling, genetic testing, and interventions to reduce cancer incidence and mortality.

**Data Extraction:** Individual investigators extracted data on participants, study design, analysis, follow-up, and results, and a second investigator confirmed key data. Investigators independently dual-rated study quality and applicability by using established criteria.

**Data Synthesis:** Five referral models accurately estimate individual risk for BRCA mutations. Genetic counseling increases the accuracy of risk perception and decreases the intention for genetic testing

among unlikely carriers and cancer-related worry, anxiety, and depression. No trials evaluated the effectiveness of intensive screening or risk-reducing medications in mutation carriers, although false-positive rates, unneeded imaging, and unneeded surgeries were higher with screening. Among high-risk women and mutation carriers, risk-reducing mastectomy decreased breast cancer by 85% to 100% and breast cancer mortality by 81% to 100% compared with women without surgery; risk-reducing salpingo-oophorectomy decreased breast cancer incidence by 37% to 100%, ovarian cancer by 69% to 100%, and all-cause mortality by 55% to 100%.

**Limitation:** The analysis included only English-language articles; efficacy trials in mutation carriers were lacking.

**Conclusion:** Studies of risk assessment, genetic counseling, genetic testing, and interventions to reduce cancer and mortality indicate potential benefits and harms that vary according to risk.

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The U.S. Preventive Services Task Force (USPSTF) recommended in 2005 that women whose family histories are associated with increased risks for clinically significant, or deleterious, mutations in the *BRCA1* or *BRCA2* gene be referred for genetic counseling and evaluation for mutation testing (1). This recommendation was intended for primary prevention of cancer and applies to women without previous diagnoses of breast or ovarian cancer.

Deleterious mutations in the *BRCA1* and *BRCA2* genes are associated with increased risks for breast, ovarian, fallopian tube, and peritoneal cancer in women and breast cancer in men (2). They are also, to a lesser degree, associated with pancreatic and early-onset prostate cancer, and *BRCA2* mutations are associated with melanoma. Mutations in BRCA genes cluster in families exhibiting an autosomal dominant pattern of transmission and account for 5% to 10% of cases of breast cancer overall (3, 4).

Specific BRCA mutations, known as founder mutations, occur among certain ethnic groups, including Ashkenazi Jewish (5–7), black (8), and Hispanic persons (9, 10), and in identified families (11–15). Other genes are associated with hereditary susceptibility to breast and ovarian cancer but are not commonly tested, such as *PTEN*

(the Cowden syndrome) and *TP53* (the Li–Fraumeni syndrome) (2, 16).

Genetic risk assessment and testing involve determining individual risk for BRCA mutations, followed by selective testing of high-risk persons. Characteristics associated with an increased likelihood of BRCA mutations (17–20) include breast and ovarian cancer in relatives and a young age of onset. These and other individual and family characteristics can be used to assess personal mutation risk and the need for referral for additional evaluation. Genetic counseling is the process of identifying and counseling persons at risk for familial or inherited cancer and is recommended before testing (21, 22).

Guidelines recommend testing for mutations only when an individual has a personal or family history of cancer suggestive of inherited cancer susceptibility and the

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results can be adequately interpreted and will aid in management (23). The type of mutation analysis that is required depends on family history. Persons without links to families or groups with known mutations (5–10, 12–14) generally have direct DNA sequencing. For appropriate candidates, interventions to reduce cancer risk include earlier, more frequent, or intensive cancer screening; risk-reducing medications; and risk-reducing surgery, including bilateral mastectomy and salpingo-oophorectomy.

This systematic review is an update of a prior review (1, 24, 25) for the USPSTF on the effectiveness and adverse effects of risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women. Its purpose is to evaluate and summarize research addressing specific key questions important to the USPSTF as it considers new recommendations for primary care practice.

## METHODS

This research is part of a comprehensive systematic review that includes an additional analysis of studies of the prevalence and penetrance of BRCA mutations that is not included in this manuscript (26). We followed a standard protocol consistent with the Agency for Healthcare Research and Quality (AHRQ) methods for systematic reviews (27). On the basis of evidence gaps identified from a prior review (24, 25), the USPSTF and AHRQ determined the key questions for this update by using the methods of the USPSTF (28). Investigators created an analytic framework incorporating the key questions and outlining the patient populations, interventions, outcomes, and potential adverse effects (**Appendix Figure 1**, available at [www.annals.org](http://www.annals.org)). A work plan was externally reviewed and modified.

The target population includes women without cancer or known BRCA mutations who are seen in clinical settings applicable to U.S. primary care practice, although the ideal candidate for mutation testing could be a male or female relative with cancer. The conditions of interest are mutation carrier status and BRCA-related cancer (predominantly breast, ovarian, fallopian tube, and peritoneal). Although other types of cancer are also considered during familial risk assessment, studies with these cancer outcomes are outside the scope of this review.

## Data Sources

We searched MEDLINE from 2004 to 30 July 2013, the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews from 2004 through the second quarter of 2013, and Health Technology Assessment during the fourth quarter of 2012 for relevant English-language studies, systematic reviews, and meta-analyses. We manually reviewed reference lists of articles and reviewed citations of key studies by using Scopus.

## Study Selection

Research published in 2004 or later and done in the United States or in populations that receive services and interventions applicable to medical practice in the United States was reviewed. Randomized, controlled trials (RCTs); systematic reviews; prospective and retrospective cohort studies; case-control studies; and diagnostic accuracy evaluations were included if they addressed the accuracy of risk assessment methods, outcomes of genetic counseling and testing, and the effectiveness of interventions to reduce BRCA-related cancer and mortality among mutation carriers.

Risk assessment methods were included if they were designed to guide referrals to genetic counselors or other genetic specialists and were usable by nonspecialists in genetics in clinical settings (that is, methods that were brief and nontechnical and did not require special training to administer or interpret). Evaluation of comprehensive models used in the practice of genetic counseling was outside the scope of this review, which focuses on primary care practice. Interventions included intensive screening, risk-reducing medications, and risk-reducing surgery. Only risk-reducing medications approved by the U.S. Food and Drug Administration (that is, tamoxifen and raloxifene) were considered, consistent with the scope of the USPSTF.

Studies of any design were included if they described potential adverse effects, including inaccurate risk assessment; inappropriate testing; false-positive and false-negative results; false reassurance; incomplete testing; misinterpretation of results; anxiety; cancer-related worry; immediate and long-term harms associated with interventions; and ethical, legal, and social implications. For adverse effects of interventions, studies were included that enrolled women at high risk for BRCA-related cancer regardless of their mutation status.

After an initial review of abstracts, we reviewed full-text articles by using additional inclusion criteria. Studies from the prior review that met inclusion criteria for the update were included to build on previous relevant research. **Appendix Figure 2** (available at [www.annals.org](http://www.annals.org)) shows the results of the search and selection process.

## Data Abstraction and Quality Assessment

An investigator abstracted data about the study design and setting; participant characteristics; procedures for data collection; number of participants enrolled and lost to follow-up; methods of exposure and outcome ascertainment; analytic methods, including adjustment for confounders; and outcomes. A second investigator confirmed the accuracy of key data. Two investigators used predefined criteria for RCTs; systematic reviews; and cohort, case-control, and diagnostic accuracy studies developed by the USPSTF (28, 29) to rate the quality of studies (good, fair, or poor) and resolved discrepancies by consensus.

Quality could not be assessed for many studies with designs that did not have predefined criteria, such as de-

scriptive, cross-sectional, and pre-post studies, and case series. The applicability of studies was determined using the population, intervention, comparator, outcomes, timing of outcomes measurement, and setting format adapted to this topic (30).

### Data Synthesis and Analysis

Because of heterogeneity across studies, results were not combined in a quantitative meta-analysis. We assessed the aggregate quality of the body of evidence (good, fair, or poor) by using methods that the USPSTF developed on the basis of the number, quality, and size of studies and consistency of results between studies (28). Studies were considered consistent if outcomes were generally in the same direction of effect and ranges of effect sizes were narrow.

### Role of the Funding Source

This research was funded by the AHRQ. Investigators worked with AHRQ staff and USPSTF members to define the scope, analytic framework, and key questions; resolve issues arising during the project; and review the final report to ensure that it met basic methodological standards for systematic reviews. The draft report was reviewed by content experts, USPSTF members, AHRQ program officers, and collaborative partners and was posted for public comment for 4 weeks during April 2013. The funding source had no role in the selection, critical appraisal, or synthesis of evidence. The investigators were solely responsible for the content and the decision to submit the manuscript for publication.

## RESULTS

### Accuracy and Adverse Effects of Referral Models to Estimate Individual Risk for BRCA Mutations

Risk models estimate the likelihood of BRCA mutations in individual persons, and some were developed to guide patient referrals to genetic counselors or other genetic specialists for more comprehensive evaluations. Ten studies describing performance characteristics of the Ontario Family History Assessment Tool (FHAT) (31–33), Manchester scoring system (33–36), Referral Screening Tool (RST) (37, 38), Pedigree Assessment Tool (PAT) (39), and Family History Screen-7 (FHS-7) (40) met inclusion criteria for this review (**Appendix Table 1**, available at [www.annals.org](http://www.annals.org)). Included studies met criteria for fair or good quality and determined the sensitivity and specificity of models by comparing results of mutation carriers versus noncarriers or referral models versus more complex models, such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (41, 42), BRCAPRO (43–45), and Myriad II (18) (**Appendix Table 2**, available at [www.annals.org](http://www.annals.org)). No studies described adverse effects of the risk models. Studies of the RST, PAT, and FHS-7 were published after the prior USPSTF systematic review.

Models were evaluated in patient populations in the United States (RST and PAT), Canada (FHAT), the United Kingdom (Manchester scoring system), and Brazil (FHS-7). Most studies defined the referral threshold as 10% estimated probability of a BRCA mutation. The FHAT and Manchester scoring system were evaluated in selected populations of known mutation carriers and noncarriers. Sensitivity was high for both models in most studies (94% for the FHAT [31, 32] and 87% to 93% for the Manchester scoring system [34–36]). Lower sensitivity estimates (70% for the FHAT and 58% for the Manchester scoring system) came from a study of both models that included 200 mutation carriers and 100 noncarriers (33), which represented a patient spectrum different from that of the other studies.

The RST, PAT, and FHS-7 were evaluated in large samples of women having screening mammography or visiting primary care clinics. The sensitivity of the RST was high compared with that of the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (89%), BRCAPRO (91%), and Myriad II (91%) (37). A revised Web-based version that includes more information on family history reported slightly higher sensitivity values (38). The PAT had 100% sensitivity compared with Myriad II (39), and the FHS-7 had 88% sensitivity compared with a genetic evaluation that included kindred analysis, risk estimates using multiple models, and clinical criteria (40).

### Benefits and Adverse Effects of Genetic Counseling to Determine Eligibility for Genetic Testing

Twenty-seven studies met inclusion criteria, including 16 published since the prior review (46–63) and 11 included previously (64–74) (**Appendix Table 3**, available at [www.annals.org](http://www.annals.org)). Studies provided data about accuracy of risk perception; intention for genetic testing; and distress, measured as breast cancer–related worry, anxiety, or depression.

#### Risk Perception

Although studies included in the prior USPSTF review were inconclusive (64, 66–69, 71–74), 8 new studies consistently reported improved accuracy of the perception of risk for breast cancer after genetic counseling (50, 54–56, 58, 59, 61, 72). A single study reported decreased accuracy (51). Only 1 study evaluated perception of risk for ovarian cancer and reported decreased accuracy after counseling (57). A fair-quality systematic review of 19 studies published before February 2007 indicated that risk perception was accurate for 42% of women before counseling and for 58% after (63). Accuracy improved when counseling provided information about family history, heredity, and personal risk estimates and facilitated informed decision making and adaptation to personal risk.

**Intention to Participate in Genetic Testing**

Two new studies reported decreased intention to have genetic testing after genetic counseling among women unlikely to be carriers (50, 55), which is consistent with prior studies (64, 67, 70). These include a study comparing telephone counseling, in-person counseling, and no counseling that indicated that women in the 2 counseling groups were less likely to pursue genetic testing than those in the non-counseling group (55). A fair-quality RCT reported decreased interest in genetic testing 6 months after group and individual counseling compared with no counseling (50).

**Cancer-Related Worry, Anxiety, and Depression**

No new studies reported increased breast cancer-related worry among women who received genetic counseling, and 8 studies reported decreases (48, 50–53, 55, 56, 60); 1 poor-quality RCT reported no changes (49). These results are consistent with prior studies indicating that breast cancer-related worry usually decreases after genetic counseling (65–67, 69–71, 73, 74). No studies reported statistically significant increases in anxiety and depression after genetic counseling; 3 reported statistically significant decreases (52, 61, 62), and 3 reported no changes (48, 56, 60). Studies in the prior review also indicated that measures of anxiety and depression generally decreased or did not differ with counseling (65, 66, 68, 69, 72–74).

**Adverse Effects of Genetic Testing**

Thirteen new observational studies (75–89) and 1 included previously (90) (Appendix Table 4, available at [www.annals.org](http://www.annals.org)) provided data about distress due to BRCA testing, measured as breast cancer-related worry, anxiety, or depression or other psychosocial outcomes. No studies described other adverse effects of testing, such as false-positive or false-negative results or unneeded risk-reducing interventions.

Five studies reported statistically significant increases in breast cancer-related worry after receipt of BRCA test results (76, 87–90). These results were confined to mutation carriers before versus after testing (88), mutation carriers compared with noncarriers (87, 89) or compared with women who were not tested (90), and women with a family history that indicates high risk for breast cancer compared with untested low-risk women (76). One study reported a decrease in breast cancer-related worry for both carriers and noncarriers (78).

Studies reported decreased anxiety scores after testing regardless of mutation status (75) and among noncarriers only (82). Prospective cohort studies found statistically significantly higher anxiety scores for mutation carriers versus noncarriers (83, 87), women with family histories of breast cancer who were not tested versus mutation carriers (79, 80), and mutation carriers and noncarriers (78). Although all women in 1 study had high anxiety scores, noncarriers had lower anxiety scores at 1-week follow-up than carriers and women who were not tested (90). Four studies re-

ported no differences in anxiety over 1 year (77, 85) or among carriers, noncarriers, and age-matched control participants (76, 84).

Women with family histories of breast cancer who did not have genetic testing had higher depression scores than mutation carriers in 1 study, although scores did not reach the threshold for clinical depression (80). Noncarriers had lower depression scores at 4-month follow-up than carriers and women who were not tested in another study (90). Four studies reported no differences in depression over time (75, 85) or among carriers, noncarriers, and age-matched control participants (76, 84), with all scores below the case threshold.

Mutation carriers had more subjective sleep problems than noncarriers and age-matched control participants, although actual sleep duration, latency, and wakefulness, as measured by a wrist monitor, showed no differences among groups (86).

**Effectiveness and Adverse Effects of Risk-Reducing Interventions in BRCA Mutation Carriers****Intensive Screening**

**Breast Cancer.** No studies of the effectiveness of intensive screening met inclusion criteria. Five studies that enrolled mutation carriers and other high-risk women described adverse effects (91–95). The Dutch MRISC (Magnetic Resonance Imaging [MRI] Screening) study reported statistically significantly higher false-positive rates with MRI than with mammography on the first and subsequent screening rounds (first, 14.0% vs. 5.5%; subsequent, 8.2% vs. 4.6%;  $P < 0.001$  for both comparisons) (91). False-negative rates for MRI were lower than those for mammography, although numbers were small (91). A study of every-6-month screening found similar false-positive rates for MRI (11%) and mammography (15%) (92). Recall rates for annual MRI were higher than those for annual mammography in a descriptive study conducted in the United Kingdom (MRI, 11.0% per woman-year; mammography, 3.9%; combined, 13.0%) (93). In that study, 245 of 279 total recalls were for benign findings, amounting to 8.5 recalls per cancer case detected.

These studies also reported additional imaging procedures or biopsies that may have been unnecessary because final results were benign and women may never have had these procedures if the original screening test had not been done (92, 96). In the Dutch MRISC study, 43% of women with unneeded biopsies had preceding screening MRIs and 28% had mammography (96). Alternating MRI with mammography screening every 6 months yielded a greater proportion of unneeded imaging (targeted ultrasonography) in women screened with mammography than with MRI (mammography, 8 of 11; MRI, 4 of 8), although rates of unneeded biopsies were similar (mammography, 3 of 11; MRI, 2 of 8) (92).

Discomfort, pain, and anxiety of women having intensive screening with annual mammography, MRI, and bi-

annual clinical breast examination were similar to those of women having only biannual clinical breast examination in a fair-quality prospective cohort study (94). Most women had no anxiety after each type of screening. In a pre-post study of screening with MRI, mammography, ultrasonography, and clinical breast examination, women who were recalled reported higher anxiety scores approximately 1 month after screening than those who were not recalled (8.8 vs. 5.9;  $P = 0.03$ ) (95). Among-group differences were not statistically significant after 6 months.

**Ovarian Cancer.** No studies of the effectiveness of intensive screening met inclusion criteria. Adverse effects were described in a study of annual measurements of serum cancer antigen-125 (CA-125) and transvaginal ultrasonography in 459 BRCA mutation carriers (mean, 2.4 screening visits [1.6 per year]) (97). Abnormalities were detected in 3% (38 of 1116) of screening visits. Of 26 diagnostic procedures, cancer was not detected in 67% (4 of 6) after abnormal serum CA-125 measurement compared with 100% (9 of 9) after abnormal transvaginal ultrasound. Combined methods resulted in an unneeded rate of diagnostic surgery of 55% (6 of 11) (97). In a study of screening with annual serum CA-125 measurements and transvaginal ultrasonography, women with abnormal results had statistically significantly higher cancer-related distress 1 week after receiving results than those with normal results, although long-term distress, anxiety, and depression scores were not higher (98).

### Risk-Reducing Medications

**Breast Cancer.** No trials evaluated the efficacy of risk-reducing medications in BRCA mutation carriers, although placebo-controlled trials of tamoxifen and raloxifene indicated reduced risk for estrogen receptor-positive breast cancer for women at various risk levels (26, 99, 100).

Adverse effects for trial participants are relevant to mutation carriers. Women using tamoxifen and raloxifene had more thromboembolic events than women using placebo (tamoxifen risk ratio [RR], 1.93 [95% CI, 1.41 to 2.64]; 4 trials and raloxifene RR, 1.60 [CI, 1.15 to 2.23]; 2 trials) (99, 100). Coronary heart disease events and stroke were not increased in placebo-controlled trials, although women randomly assigned to raloxifene had higher stroke mortality than placebo recipients in the RUTH (Raloxifene Use for the Heart) trial (RR, 1.49 [CI, 1.00 to 2.24]) (101). Tamoxifen caused more cases of endometrial cancer (RR, 2.13 [CI, 1.36 to 3.32]; 3 trials) and was related to more benign gynecologic conditions; surgical procedures, including hysterectomy; and uterine bleeding than placebo (99, 100). Women receiving tamoxifen had more cataract surgeries than those receiving placebo in the NSABP (National Surgical Adjuvant Breast and Bowel Project) P-1 trial (102). The most common adverse effects were vasomotor symptoms and vaginal discharge, itching, or dryness

for tamoxifen and vasomotor symptoms and leg cramps for raloxifene (99, 100).

### Risk-Reducing Surgery

**Bilateral Mastectomy.** A prospective cohort study of women with BRCA mutations indicated that none of 75 women with risk-reducing mastectomies was diagnosed with breast cancer during follow-up compared with 34 of 585 (5.8%) without mastectomies (103). A cohort study of mutation carriers in Denmark found that 3 of 96 women who had mastectomies were diagnosed with breast cancer versus 16 of 211 who did not (hazard ratio [HR], 0.39 [CI, 0.12 to 1.36]), although the study was inadequately powered for this outcome (104). A descriptive study found that none of 307 women who had BRCA mutations or were otherwise considered to be at high risk and had mastectomies was diagnosed with breast cancer during follow-up, whereas 21.3 were expected (105), consistent with results of an earlier study of 18 mutation carriers (106, 107).

Adverse effects include surgical complications, long-term physical effects, and distress. In a case series of 122 women who had risk-reducing mastectomy, 64.4% reported postsurgical numbness, pain, tingling, infection, swelling, breast hardness, bleeding, organizing hematoma, failed reconstruction, breathing problems, thrombosis, and pulmonary embolism (108). Most women (87.3%) reported postmastectomy pain and discomfort, and 21.8% reported that pain affected their daily lives in a follow-up study of 59 high-risk women (109). Women's pain scores did not statistically significantly differ before mastectomy, 6 months after mastectomy, and 1 year after mastectomy in another study (110).

In a study of 90 high-risk women with risk-reducing bilateral mastectomies, including 50 mutation carriers, anxiety scores statistically significantly decreased after surgery (mean Hospital Anxiety and Depression Scale scores: before surgery, 5.59; 6 months after surgery, 3.80; 1 year after surgery, 3.83;  $P < 0.001$ ) (110, 111). Women also reported less pleasure in sexual activity 1 year after surgery than 6 months after surgery and before surgery (mean Sexual Activity Questionnaire scores: before surgery, 12.28; 6 months after surgery, 12.21; 1 year after surgery, 11.18;  $P = 0.005$ ). Depression scores, body image, and other concerns did not change. Other studies indicated no statistically significant changes in psychological or sexual activity measures after mastectomy (108, 109, 112).

**Salpingo-Oophorectomy and Oophorectomy.** In a prospective study of 1557 BRCA mutation carriers, salpingo-oophorectomy was statistically significantly associated with reduced incidence of ovarian or primary peritoneal cancer (1.3% vs. 5.8%; HR, 0.28 [CI, 0.12 to 0.69]), breast cancer (11.6% vs. 21.6%; HR, 0.54 [CI, 0.37 to 0.79]), and all-cause mortality (1.8% vs. 5.9%; HR, 0.45 [CI, 0.21 to 0.95]) (103). In this study, salpingo-oophorectomy did not reduce breast cancer- and ovarian cancer-specific mortal-

ity, although the study may have been underpowered for these outcomes. Oophorectomy was also associated with reduced breast cancer incidence in a prospective study of women from families with known *BRCA1* mutation carriers (18% vs. 42%; HR, 0.38 [CI, 0.15 to 0.97]) (113). Risk reduction was most pronounced for women who had the procedure at younger ages in this study, as well as in a retrospective study of risk-reducing oophorectomy (114).

Few studies described adverse effects. Most women reported worse vasomotor symptoms and sexual function after risk-reducing salpingo-oophorectomy in a small pre-post study of mutation carriers (115). In another small pre-post study, mutation carriers reported an increase in somatization; a decrease in cancer-related distress; and no change in health-related quality of life, anxiety, or depression after salpingo-oophorectomy (116).

## DISCUSSION

No studies directly addressed the effectiveness of risk assessment, genetic counseling, and genetic testing in reducing cancer incidence and mortality (Table). Five referral models accurately estimated individual risk for BRCA mutations, with most sensitivity measures greater than 85%. However, reference standards and study designs varied, and some models have been evaluated only in single studies. Risk was based on self-reported information, which potentially compromises model accuracy. The sensitivity and specificity of self-reported history of cancer in first-degree relatives have been estimated as 65% and 99% for breast cancer (117) and 50% and 99% for ovarian cancer, respectively (118).

Genetic counseling increases the accuracy of risk perception; decreases intention for mutation testing among women who are unlikely carriers; and decreases cancer-related worry, anxiety, and depression. Limitations of studies included differences in designs and measures, dissimilar comparison groups, and small sizes. Risk perception improved after receipt of test results, and breast cancer-related worry and anxiety increased for women with positive results and decreased for others, although results were inconsistent. Studies were limited by high loss to follow-up and differences between comparison groups. Other relevant adverse effects of genetic testing were not studied, including false-positive or false-negative results, genetic discrimination, and insurability.

No trials evaluated the effectiveness of intensive screening in reducing the incidence of BRCA-related cancer and mortality. Higher rates of false-positive test results, unneeded imaging, and unneeded surgeries with screening were reported. No trials of risk-reducing medications provided results for BRCA mutation carriers, and whether efficacy in carriers differs from that in noncarriers is unclear. In trials, tamoxifen and raloxifene increased thromboembolic events and tamoxifen increased endometrial cancer

and cataracts. Both caused undesirable effects for some women, such as vasomotor symptoms.

For high-risk women and mutation carriers, risk-reducing bilateral mastectomy reduced breast cancer incidence and mortality and oophorectomy or salpingo-oophorectomy reduced breast and ovarian cancer incidence and all-cause mortality. Comparison groups varied among studies, although results were consistent. Some women had physical complications of risk-reducing surgery, postsurgical symptoms, or changes in body image, whereas some women had less anxiety. Studies were descriptive and lacked important outcomes, and the few available studies had small numbers of participants and no comparison groups.

Limitations of this review include the use of only English-language articles and studies applicable to the United States, although these studies are most relevant to the USPSTF. The review focused on 5 key questions that restricted its scope, and men were not explicitly included except as family members of the women under evaluation. The number, quality, and applicability of included studies varied widely. Data were not available to determine the optimum age for testing and how the age at testing influences benefits and harms. Whether testing for BRCA mutations reduces cause-specific or all-cause mortality and improves quality of life is unknown. The harms associated with receiving a false-negative result or a result indicating mutations of unknown significance are unknown. Evidence of harms often relied on small descriptive studies with brief follow-up, and the long-term effect of risk assessment, counseling, and testing is unknown.

Several factors not evaluated in studies influence treatment effects. Effectiveness of salpingo-oophorectomy for reducing breast cancer risk depends on the age at which the procedure is done and decreases after menopause. However, how and when the benefit-harm ratio shifts for women facing this decision is uncertain. Also, the type of risk-reducing intervention that a mutation carrier selects may depend on her specific mutation. For example, women with *BRCA1* mutations have higher risks for ovarian cancer than those with *BRCA2* mutations (119, 120) and may consider their surgical options differently. Medications reduce risk for estrogen receptor-positive breast cancer (100) and consequently may be a more favorable choice for women with *BRCA2* mutations, for whom 77% of breast cancer cases are estrogen receptor-positive (121). How these factors influence patient decision making and eventual clinical outcomes is unknown.

To determine the appropriateness of risk assessment and testing for BRCA mutations in primary care, research on access to testing; effectiveness of screening approaches, including risk stratification; use of system supports; and patient acceptance and education is needed. Trials comparing types of providers and protocols could address who should perform these services, how they should be performed, and what skills are required. The consequences of

Table. Summary of Evidence

New Studies*	Design	Limitation	Consistency	Applicability	Overall Quality	Finding
<b>Effectiveness of risk assessment, genetic counseling, and genetic testing to reduce BRCA-related cancer and mortality</b>						
None	—	—	—	—	—	—
<b>Accuracy and adverse effects of referral models to estimate individual risk for BRCA mutations</b>						
8 studies of 5 models; no studies of adverse effects	Diagnostic accuracy	Reference standards and study designs varied; risk was based on self-reported information	Consistent	High	Good	Risk models report sensitivity estimates >85% for the FHAT, Manchester scoring system, RST, PAT, and FHS-7.
<b>Benefits and adverse effects of genetic counseling to determine eligibility for genetic testing</b>						
16 studies of the accuracy of risk perception, intention for genetic testing, and distress	RCT, cohort, case-control, pre-post	Noncomparable groups; small size; outcome measures varied	Consistent	High	Fair	Counseling increased the accuracy of risk perception and decreased intention for mutation testing among unlikely carriers as well as cancer-related worry, anxiety, and depression.
<b>Adverse effects of genetic testing</b>						
13 studies of risk perception and distress	Cohort, case-control, pre-post	No studies of other outcomes; high loss to follow-up; comparison groups and measures varied	Mixed	High	Fair	Breast cancer-related worry and anxiety increased for women with positive results and decreased for others, although results differed across studies. Risk perception improved after receipt of test results.
<b>Effectiveness of risk-reducing interventions</b>						
No studies of intensive screening or risk-reducing medications among BRCA mutation carriers	—	—	—	—	—	—
Risk-reducing surgery: 3 studies of mastectomy and 3 of oophorectomy or salpingo-oophorectomy	Cohort	Comparison groups varied	Consistent	High	Fair	For high-risk women, including mutation carriers, mastectomy reduced breast cancer by 85% to 100% and breast cancer mortality by 81% to 100%; salpingo-oophorectomy reduced breast cancer by 37% to 100%, ovarian cancer by 69% to 100%, and all-cause mortality by 55% to 100%.
<b>Adverse effects of risk-reducing interventions in BRCA mutation carriers</b>						
Intensive screening: 3 studies of physical harms of breast cancer screening and 2 of anxiety; 1 study of physical harms of ovarian cancer screening and 1 of cancer-related distress	Cohort	No RCTs; screening intervals and false-positive calculations varied among studies; some studies lacked within-cohort comparison groups	Consistent	High	Poor	False-positive rates, unnecessary imaging, and unneeded surgeries were higher with screening. Some women had transient cancer-related distress or anxiety if screening results were abnormal.

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New Studies*	Design	Limitation	Consistency	Applicability	Overall Quality	Finding
Risk-reducing medications: 6 placebo-controlled trials (4 of tamoxifen and 2 of raloxifene) and 1 head-to-head trial in a systematic review	RCT	No results for BRCA mutation carriers; trials were heterogeneous; data on long-term effects were incomplete	Consistent	High	Good	Tamoxifen and raloxifene increased thromboembolic events compared with placebo. Tamoxifen increased endometrial cancer and cataracts compared with raloxifene. Both caused adverse effects for some women.
Risk-reducing surgery: 6 studies of complications, physical effects, or distress	Case series, pre-post	Lack of studies; small numbers of participants; no comparison groups	NA	Low	Poor	Some women had physical complications of surgery, postsurgical symptoms, changes in body image, and less anxiety.

FHAT = Ontario Family History Assessment Tool; FHS-7 = Family History Screen-7; NA = not applicable; PAT = Pedigree Assessment Tool; RCT = randomized, controlled trial; RST = Referral Screening Tool.  
\* Studies published in 2004 or later.

identifying women as high-risk, as well as genetic testing of women and their relatives, require more study. Well-designed investigations using standardized measures and enrolling participants that reflect the general population, including women from minority groups, are needed.

An expanded database or registry of patients receiving genetic counseling and testing for BRCA mutations would provide essential information about predictors of cancer, response to interventions, and other modifying factors. Traditionally, all patients clinically tested through direct DNA sequencing in the United States used a single private laboratory and patient data were inaccessible. Developing a centralized accessible database with key variables to address these issues as testing practices change in the wake of the recent U.S. Supreme Court decision on DNA patents (122) would be a major advance in this field.

Additional research on interventions is needed. Practice standards for screening have preceded supporting evidence despite known harms of overscreening. For example, although intensive screening with annual transvaginal ultrasonography and serum CA-125 measurement is recommended for high-risk women (21), no efficacy trials are available. The PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial reported no mortality benefit of screening average-risk women by using transvaginal ultrasonography and serum CA-125 measurement compared with usual care after 12 years of follow-up (123) and did not report outcomes for high-risk women, including BRCA mutation carriers. Also, a study of 3532 European women who were at increased risk for ovarian cancer, had unknown BRCA status, received transvaginal ultrasonography and CA-125 measurement, and were followed for up to 16 years indicated no stage shifts in disease incidence (124).

Trials of risk-reducing medications in mutation carriers, including aromatase inhibitors, and measurement of

long-term outcomes are also needed. Comparisons of salpingo-oophorectomy versus more limited surgeries, such as salpingectomy alone, would inform current practice. Studies of factors related to acceptance of risk-reducing interventions based on genetic information would be useful, such as determining whether cancer incidence in relatives is reduced because they adopt risk-reducing interventions. This information could improve patient decision making and lead to better health outcomes.

The process of risk assessment and referral, evaluation by genetic counselors, genetic testing, and use of intensive screening and risk-reducing medications and surgeries is complex. Each step requires careful interpretation of information, consideration of risks, weighing of benefits and harms, and shared decision making before moving to the next step. Services must be well-integrated and highly personalized to optimize benefits and minimize harms for women as well as their families. Additional studies are necessary to better inform practice.

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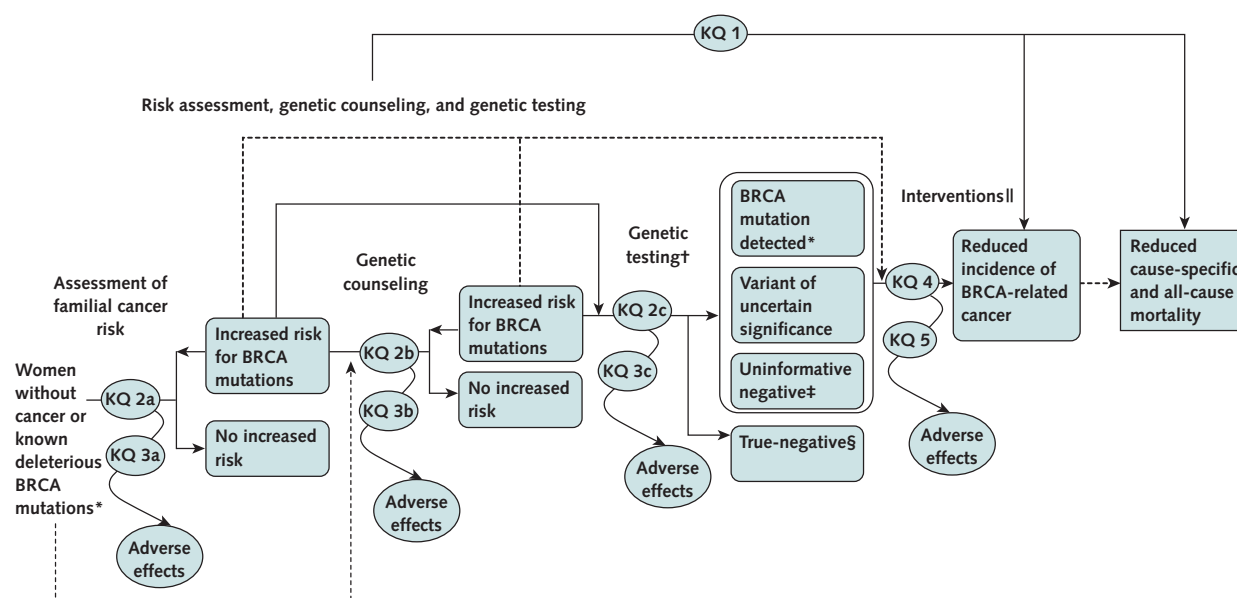
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Appendix Figure 1. Analytic framework and key questions.



#### Key Questions

1. Do risk assessment, genetic counseling, and genetic testing lead to reduced incidence of BRCA-related cancer and reduced cause-specific and all-cause mortality?
- 2a. What is the accuracy of methods to assess familial cancer risk for BRCA-related cancer when done by a nonspecialist in genetics in a clinical setting?
- 2b. What are the benefits of genetic counseling in determining eligibility for genetic testing for BRCA-related cancer? Potential benefits include improved accuracy of risk assessment and pretest probability for testing and improved patient knowledge, risk perception, satisfaction, and health and psychological outcomes.
- 2c. Among women with increased risk for BRCA-related cancer, what is the clinical validity of genetic testing for deleterious mutations?
3. What are the potential adverse effects of 3a) risk assessment, 3b) genetic counseling, and 3c) genetic testing? Adverse effects include, but may not be limited to, inaccurate risk assessment; inappropriate testing; false-positive and false-negative results; adverse effect on the patient's relationships with family; false reassurance; incomplete testing; misinterpretation of the test result; anxiety; worry about cancer; and ethical, legal, and social implications.
4. Do interventions reduce the incidence of BRCA-related cancer and death for women with increased risk? Interventions include intensive screening (earlier and more frequent mammography and breast MRI), use of risk-reducing medications (tamoxifen and raloxifene), and risk-reducing surgery (mastectomy and salpingo-oophorectomy).
5. What are the potential adverse effects of interventions to reduce risk for BRCA-related cancer? Adverse effects include, but may not be limited to, immediate and long-term harms associated with breast imaging, risk-reducing medications, and risk-reducing surgery and ethical, legal, and social implications.

KQ = key question; MRI = magnetic resonance imaging.

\* Clinically significant mutations of the *BRCA1* or *BRCA2* gene or related syndromes.

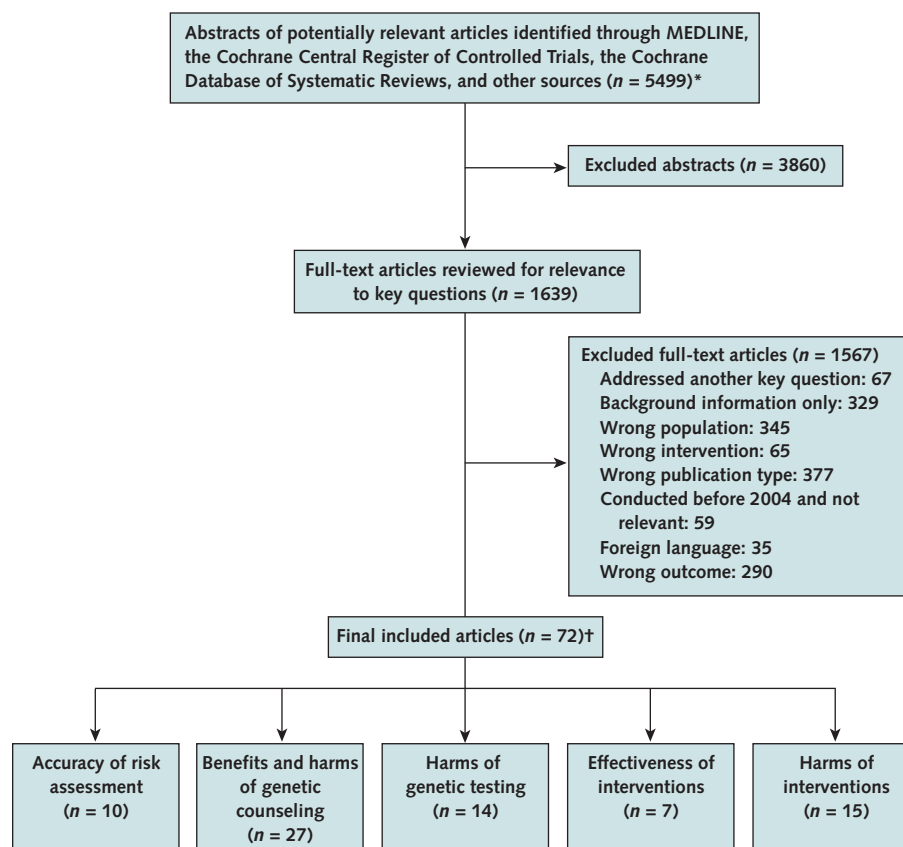
† Testing may be done on the unaffected woman, the relative with cancer, or the relative with the highest risk, as appropriate.

‡ No known mutation in relatives and none detected in the patient.

§ Known mutation in relatives but none detected in the patient.

|| Interventions include increased early detection through intensive screening (earlier and more frequent mammography and breast MRI), risk-reducing medications (tamoxifen and raloxifene), and risk-reducing surgery (mastectomy and salpingo-oophorectomy).

Appendix Figure 2. Summary of evidence search and selection.



\* Identified from reference lists, hand-searching, suggestions from experts, and other methods.

† Studies that provided data and contributed to the body of evidence were considered to be “included.” Studies may contribute data to >1 key question. This number includes studies included from the prior review as well as this updated review.

Appendix Table 1. Models Estimating Individual Risk for BRCA Mutations to Guide Referrals

Model	Data Collection and Calculation*	Relatives With Breast or Ovarian Cancer	Additional Risk Factors in Model	Accuracy Studies						
				Study, Year (Reference)	Population	Reference Standard	Sensitivity, %	Specificity, %	PPV	NPV
FHAT	Clinical scoring tool; referral threshold of 10 is equivalent to a 2-fold increase in risk for breast or ovarian cancer.	First-, second-, and third-degree	Age at diagnosis, bilateral breast cancer, breast and ovarian cancer in the same person, breast cancer in men, colon and prostate cancer	Gilpin et al, 2000 (31)	35 carriers and 149 noncarriers	10% threshold	94	51	0.31	0.97
				Parmigiani et al, 2007 (32)	33 carriers and 559 noncarriers	10% threshold	94	32	†	‡
				Panchal et al, 2008 (33)	200 carriers and 100 noncarriers	10% threshold	70	63	–	–
Manchester scoring system	Clinical scoring tool; referral threshold of 10 for <i>BRCA1</i> - or <i>BRCA2</i> -specific scores or 15 combined. Not intended for Ashkenazi Jewish persons.	First-, second-, and third-degree	Type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, age at diagnosis	Evans et al, 2004 (34)	23 carriers and 235 noncarriers	10% threshold	87	66	0.20	0.98
				Barcenas et al, 2006 (35)	69 carriers and 306 noncarriers	10% threshold	93	41	0.28	0.96
				Panchal et al, 2008 (33)	200 carriers and 100 noncarriers	15% threshold	58	71	–	–
				Antoniou et al, 2008 (36)	365 carriers and 1569 noncarriers	15% threshold	92	33	0.24	0.95
RST	Clinical checklist of 13 items; referral threshold of 2 positive responses.	First- and second-degree	Breast cancer in women $\leq 50$ y (self or relatives), ovarian cancer at any age (self or relatives), $\geq 2$ cases of breast cancer in women aged $> 50$ y on the same side of the family; breast cancer in men; Jewish ancestry	Bellcross et al, 2009 (37)	296 women randomly selected from 2462 tested while having screening mammography	Correctly assigns to high mutation probability compared with BOADICEA, BRCAPRO, and Myriad II models at 10% thresholds	BOADICEA: 89 BRCAPRO: 91 Myriad II: 91 Overall: 81§	BOADICEA: 77 BRCAPRO: 76 Myriad II: 78 Overall: 92§	BOADICEA: 0.28 BRCAPRO: 0.24 Myriad II: 0.34 Overall: 0.80§	BOADICEA: 0.99 BRCAPRO: 0.98 Myriad II: 0.99 Overall: 0.92§
PAT	Clinical scoring tool; optimum referral threshold of 8.	First-, second-, and third-degree	Breast cancer in women aged $\leq 50$ y or $> 50$ y, ovarian cancer at any age, breast cancer in men, Ashkenazi Jewish ancestry	Hoskins et al, 2006 (39)	737 women identified at potentially increased risk from 3906 tested while having screening mammography**	Correctly assigns to high mutation probability compared with the Myriad II model at the 10% threshold	100	93	0.63	1.00
FHS-7	Clinical checklist of 7 items; referral threshold of 1 positive response.	First-degree	Any relatives with breast cancer at age $\leq 50$ y, bilateral breast cancer, breast and ovarian cancer in the same person, breast cancer in men, $\geq 2$ relatives with breast and/or ovarian cancer, $\geq 2$ relatives with breast and/or colon cancer	Ashton-Prolla et al, 2009 (40)	885 women with $\geq 1$ positive response and 910 with no positive responses from 9218 women tested in primary care clinics	Correctly assigns to high mutation probability compared with genetic evaluation††	88	56	0.63	1.00

BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; FHAT = Ontario Family History Assessment Tool; FHS-7 = Family History Screen-7; NPV = negative predictive value; PAT = Pedigree Assessment Tool; PPV = positive predictive value; RST = Referral Screening Tool.

\* Referral threshold indicates estimated probability to initiate a referral, most set at 10%.

† Positive likelihood ratio of 1.38.

‡ Negative likelihood ratio of 0.18.

§ Defined as high-risk by any of the models.

|| Corrected for general populations: 0.39.

¶ Corrected for general populations: 0.78.

\*\* Defined as potentially at increased risk by the Gail model for 5-y risk for breast cancer of 6.7%, lifetime risk of 15%, or  $\geq 1$  case of breast or ovarian cancer in any family member.

†† Evaluation included kindred analysis, breast cancer risk estimates, Penn II *BRCA1* and *BRCA2* Mutation Risk Evaluation Model mutation risk estimate, and American Society of Clinical Oncology criteria.

*Appendix Table 2. Models Used as Reference Standards to Estimate Individual Risks for BRCA Mutations*

Model	Administration	Application	Description
BOADICEA (42, 125)	Web-based	All persons	Includes breast, ovarian, prostate, and pancreatic cancer. Family history data for first-, second-, and third-degree relatives are entered for persons with and without cancer.
BRCAPro (43–45)	CaGene computer program (126)	All persons	Includes breast cancer in men and women and ovarian cancer. Bayesian model using first- and second-degree family history includes age at diagnosis, ethnicity, and size of family to estimate the age-specific probability of a BRCA mutation. Generates conditional or posterior probabilities.
Myriad II (18)	CaGene computer program (126) or tables	All persons	Includes breast cancer in men and women and ovarian cancer. Logistic regression model developed from data on women with early-onset breast cancer and/or ovarian cancer with $\geq 2$ first- or second-degree relatives with early breast or ovarian cancer.
Penn II (127)	Web-based	Families with cases of breast cancer	Includes breast, ovarian, prostate, and pancreatic cancer. Uses a 1-page questionnaire to solicit data for first-, second-, and third-degree relatives. Determines the probability of a BRCA mutation in the person as well as family members with cancer.

BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; CaGene = Cancer Gene; Penn II = Penn II *BRCA1* and *BRCA2* Mutation Risk Evaluation Model.

Appendix Table 3. Studies of Genetic Counseling

Study, Year (Reference)	Participants, <i>n</i>	Design	Genetic Counseling Provider	Setting	Measure	Outcome					Quality Rating
						Accuracy of Risk Perception	Intention to Participate in Testing	Worry	Anxiety	Depression	
Current report											
Bennett et al, 2008 (48)	128	Pre-post	Genetic counselor	Cancer genetics service center	DUKE-SSQ, HADS, IES, MCMQ, NSI	–	–	Decrease	NS	NS	NA
Bennett et al, 2009 (47)	128	Pre-post	Genetic counselor	Cancer genetics service center	DUKE-SSQ, IES, MCMQ	–	–	NS	–	–	NA
Bloom et al, 2006 (49)	163	RCT	Counselor	Telephone counseling	NSI	NS	–	NS	–	–	Poor*†‡
Bowen et al, 2006 (50)	221	RCT	Psychologist, genetic counselor	University	NSI, BSI	Increase	Decrease	Decrease	–	–	Fair*
Brain et al, 2011 (51)	263	Pre-post	Clinician	NR	CWS-R	–	–	Decrease	–	–	NA
Braithwaite et al, 2005 (52)	72	RCT	Clinical nurse specialist	NR	NSI, STAI, HADS	Increase	–	Decrease	Decrease	–	Fair*
Fry et al, 2003 (53)	263	RCT	Genetic specialist, breast surgeon	Familial breast cancer clinic	CWS	Increase	–	Decrease	–	–	Fair\$
Gurmankin et al, 2005 (54)	125	Pre-post	Clinician	University cancer risk evaluation program	STAI, NSI	Increase	–	–	–	–	NA
Helmes et al, 2006 (55)	340	RCT	Genetic counselor	NR	NSI	Increase	Decrease	Decrease	–	–	Fair*
Hopwood et al, 2004 (56)	256	Pre-post	Genetic counselor	Cancer genetic service centers	NSI, GHQ, CWS	NS	–	Decrease	NS	–	NA
Kelly et al, 2008 (57)	78	Pre-post	Genetic counselor	NR	NSI	Decrease	–	–	–	–	NA
Matloff et al, 2006 (58)	64	RCT	Genetic counselor	NR	NSI	Increase	–	–	–	–	Fair*
Mikkelsen et al, 2007 (59)	1971	Prospective	Physician	Clinical department	IES	NS	–	–	–	–	Fair†
Mikkelsen et al, 2009 (60)	1971	Prospective	Physician	Clinical department	HADS	–	–	Decrease	NS	NS	Fair†
Pieterse et al, 2011 (61)	77	Pre-post	Clinical geneticist, genetic counselor	Department of medical genetics	VAS, NSI, PPC, STAI, IES	Increase	–	–	Decrease	–	NA
Roshanai et al, 2009 (62)	163	RCT	Specialist nurse	Cancer genetic clinic	SPIKES, HADS	Increase	–	–	Decrease	Decrease	Fair*
Prior report											
Bowen et al, 2002 (64)	354	RCT	Genetic or health counselor	NR	NSI	–	Decrease	–	–	–	Fair  ¶
Bowen et al, 2004 (65)	354	RCT	Genetic or health counselor	NR	NSI	Increase	–	NS	Decrease	NS	Fair\$¶
Brain et al, 2002 (66)	740	RCT	Clinical geneticist, genetic nurse specialist	NR	STAI, NSI	Increase	–	Mixed**	Decrease	–	Good
Burke et al, 2000 (67)	356	RCT	Genetic counselor	Medical office	NSI	Increase	Decrease	NS	–	–	Fair  ¶
Cull et al, 1998 (68)	144	RCT	Geneticist, breast surgeon	Breast cancer family clinic	NSI, STAI, GHQ	Mixed\$	–	–	NS	NS	Good
Hopwood et al, 1998 (69)	174	Prospective	Clinician	Family history clinics	NSI, GHQ, PAS	Increase	–	NS	NS	–	Fair††
Lerman et al, 1996 (71)	227	RCT	Genetic counselor	Cancer centers	IES	Increase	–	NS	–	–	Fair  ¶
Lerman et al, 1999 (70)	364	RCT	Oncology nurse, genetic counselor	Hospital cancer center	IES	–	Increase	NS	–	–	Fair\$  ¶
Lobb et al, 2004 (72)	193	Longitudinal	Clinical geneticist, oncologist, genetic counselor	NR	NSI, IES, HADS	NS	–	–	NS	NS	Good

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Appendix Table 3—Continued

Study, Year (Reference)	Participants, <i>n</i>	Design	Genetic Counseling Provider	Setting	Measure	Outcome					Quality Rating
						Accuracy of Risk Perception	Intention to Participate in Testing	Worry	Anxiety	Depression	
Watson et al, 1998 (74)	115	RCT	Clinical geneticist	Hospitals	GHQ-12, CWS, VAS	Increase	–	NS	NS	NS	Good
Watson et al, 1999 (73)	283	Prospective	Clinical geneticist	Genetic counseling centers	NSI, GHQ, IES, STAI	NS	–	NS	NS	–	Good

BSI = Brief Symptom Inventory; CWS = Cancer Worry Scale; CWS-R = Cancer Worry Scale-Revised; Duke-UNC SSQ = Duke-University of North Carolina Functional Social Support Questionnaire; GHQ = General Health Questionnaire; GHQ-12 = 12-item General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; IES = Impact of Events Scale; MCMQ = Medical Coping Modes Questionnaire; NA = not available; NR = not reported; NS = not statistically significant; NSI = Non Standard Instrument; PAS = Psychiatric Assessment Schedule; PPC = Perceived Personal Control; RCT = randomized, controlled trial; SPIKES = Setting, Patient's Perception, Invitation, Knowledge, Exploring/Empathy, Strategy/Summary; STAI = State-Trait Anxiety Inventory; VAS = visual analog scale.

\* Inadequate reporting of randomization technique (49, 50, 52, 55, 58, 62).

† Noncomparable groups at baseline (49, 59, 60).

‡ No specified eligibility criteria (49).

§ High attrition (53, 68) or attrition not reported (65).

|| Allocation concealment not reported (64, 65, 70, 71).

¶ No intention-to-treat analysis (65, 67, 70, 71).

\*\* Results varied by group.

†† Unclear whether participants were from random or consecutive groups (69).

Appendix Table 4. Studies of Distress After Genetic Testing

Study, Year (Reference)	Participants, <i>n</i>	Design	Mutation Status	Genetic Counseling Provider	Comparison	Measure	Outcome			Quality Rating
							Worry	Anxiety	Depression	
Current report										
Arver et al, 2004 (75)	63	Pre-post	Positive or negative	Genetically trained oncologist, oncology nurse	A: Before test B: 2 mo after test C: 1 y after test	HADS, SF-36	–	Decrease (B, C vs. A)	NS	NA
Dagan and Shochat, 2009 (76)	73	Case-control	Positive or negative	NR	A: Carriers B: Noncarriers C: Age-matched control participants	HRQOL, CRW, BSI	Increase (A, B vs. C)	NS	NS	Fair*
Ertmanski et al, 2009 (77)	56	Pre-post	Positive	NR	A: Before test B: 1 mo after test C: 1 y after test	STAI, IES	–	NS	–	NA
Foster et al, 2007 (78)	154	Prospective	Positive or negative	NR	A: Carriers B: Noncarriers	GHQ, CWS-R	Decrease (A, B)	Increase (A, B)	–	Fair*†
Geirdal et al, 2005 (80)	10 244	Prospective	Positive or unknown	NR	A: Positive B: Not tested but family history C: Not tested, 10 000 age-matched control participants	HADS, GHQ, BHS, IES	–	Increase (B vs. A)	Increase (B vs. A)	Good
Geirdal and Dahl, 2008 (79)	242	Prospective	Positive or unknown	NR	A: Positive B: Not tested but family history	HADS, COPE	–	Increase (B vs. A)	–	Good
Kinney et al, 2005 (82)	52	Prospective	Positive or negative	Genetic professional	A: Carriers B: Noncarriers	STAI, IES, CES-D	–	Decrease (B)	–	Poor*†
Low et al, 2008 (83)	47	Prospective	Positive or negative/uncertain	Genetic counselor	A: Positive B: True-negative and uncertain	IES-R, COPE, PTGI	–	Increase (A vs. B)	–	Fair*†‡
Metcalfe et al, 2012 (88)	17	Pre-post	Positive	NR	A: Before test B: 1 y after test C: 2 y after test	IES	Increase (B vs. A, C)	–	–	NA
Reichelt et al, 2004 (84)	209	Prospective	Positive, negative, or unknown	Medical geneticist, genetic counselor	A: Carriers B: Noncarriers	HADS, GHQ, BHS, IES	–	NS	NS	Good
Reichelt et al, 2008 (85)	181	Pre-post	Positive or true-negative	Genetic counselor	A: Before test B: 6 wk after test C: 18 mo after test	HADS, IES	–	NS	NS	NA
van Dijk et al, 2006 (87)	132	Prospective	Positive, true-negative, or uncertain	NR	A: Positive B: True-negative C: Uninformative	IES, NSI	Increase (A vs. B, C)	Increase (A vs. B, C)	–	Good
Prior report										
Meiser et al, 2002 (90)	143	Prospective	Positive or negative	NR	A: Carriers B: Noncarriers C: Not tested	BDI, IES, MBSS, STAI, NSI	Increase (A vs. C)	Decrease (B vs. A, C)	Decrease (B vs. A, C)	Good

BDI = Beck Depression Inventory; BHS = Beck Hopelessness Scale; BSI = Brief Symptom Inventory; CES-D = Center for Epidemiologic Studies-Depression Scale; COPE = Emotional Approach Coping Scale; CRW = Cancer-Related Worry Scale; CWS-R = Cancer-Related Worry Scale-Revised; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; HRQOL = Health-Related Quality of Life; IES = Impact of Events Scale; IES-R = Impact of Events Scale-Revised; MBSS = Miller Behavioral Style Scale; NA = not applicable; NR = not reported; NS = not statistically significant; NSI = Non Standard Instrument; PTGI = Post-Traumatic Growth Inventory; SF-36 = Swedish 36-Item Short Form Health Survey; STAI = State-Trait Anxiety Inventory.

\* Unclear enrollment (76, 78, 82, 83).

† Differences between groups at baseline or lack of reporting of baseline participant characteristics (78, 82, 83).

‡ High loss to follow-up (83).