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, 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 estimated individual risk for BRCA mutations. Genetic counseling increased 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 incidence and mortality indicate potential benefits and harms that vary according to risk.

Primary Funding Source: Agency for Healthcare Research and Quality.

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 young age at 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
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). 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 could be used 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) 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-
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 BOADICEA (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). 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 noncounseling 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) 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 findings 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 family histories that indicate 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).

Although some studies reported decreased anxiety scores after testing regardless of mutation status (75) and among noncarriers only (82), others 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 reported 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), although 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 ultrasonography. 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 specifically, 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 participants are of placebo-controlled trials relevant to mutation carriers. Women using tamoxifen and raloxifene had more thromboembolic events than women using placebo (tamoxifen risk ratio \([RR] = 1.93 \ [95\% CI, 1.41 \text{ to } 2.64] \); 4 trials and raloxifene \([RR] = 1.60 \ [CI, 1.15 \text{ to } 2.23]) \); 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 \((RR = 1.49 \ [CI, 1.00 \text{ to } 2.24]) \) (101). Tamoxifen caused more cases of endometrial cancer \((RR = 2.13 \ [CI, 1.36 \text{ to } 3.32]) \); 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 symp-

toms 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 \([HR] = 0.39 \ [CI, 0.12 \text{ to } 1.36]) \), 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). In another study, women’s pain scores did not statistically significantly differ before mastectomy, 6 months after mastectomy, or 1 year after mastectomy (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%; \([HR] = 0.28 \ [CI, 0.12 \text{ to } 0.69]) \), breast cancer (11.6% vs. 21.6%; \([HR] = 0.54 \ [CI, 0.37 \text{ to } 0.79]) \), and all-cause mortality (1.8% vs. 5.9%; \([HR] = 0.45 \ [CI, 0.21 \text{ to } 0.95]) \) (103). In this study, salpingo-oophorectomy did not
reduce breast cancer– and ovarian cancer–specific mortality, 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 has not been studied. 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 effects are 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 done, and what skills are required. The consequences of identi-
### Table. Summary of Evidence

<table>
<thead>
<tr>
<th>New Studies*</th>
<th>Design</th>
<th>Limitation</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall Quality</th>
<th>Finding</th>
</tr>
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<tbody>
<tr>
<td>Effectiveness of risk assessment, genetic counseling, and genetic testing to reduce BRCA-related cancer and mortality</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Accuracy and adverse effects of referral models to estimate individual risk for BRCA mutations</td>
<td>8 studies of 5 models; no studies of adverse effects</td>
<td>Diagnostic accuracy</td>
<td>Reference standards and study designs varied; risk was based on self-reported information</td>
<td>Consistent</td>
<td>High</td>
<td>Good</td>
</tr>
<tr>
<td>Benefits and adverse effects of genetic counseling to determine eligibility for genetic testing</td>
<td>16 studies of the accuracy of risk perception, intention for genetic testing, and distress</td>
<td>RCT, cohort, case–control, pre–post</td>
<td>Noncomparable groups; small size; outcome measures varied</td>
<td>Consistent</td>
<td>High</td>
<td>Fair</td>
</tr>
<tr>
<td>Adverse effects of genetic testing</td>
<td>13 studies of distress</td>
<td>Cohort, case–control, pre–post</td>
<td>No studies of other outcomes; high loss to follow-up; comparison groups and measures varied</td>
<td>Mixed</td>
<td>High</td>
<td>Fair</td>
</tr>
<tr>
<td>Effectiveness of risk-reducing interventions</td>
<td>No studies of intensive screening or risk-reducing medications among BRCA mutation carriers</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Risk-reducing surgery: 3 studies of mastectomy and 3 of oophorectomy or salpingo-oophorectomy</td>
<td>Cohort</td>
<td>Comparison groups varied</td>
<td>Consistent</td>
<td>High</td>
<td>Fair</td>
<td>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%.</td>
</tr>
<tr>
<td>Adverse effects of risk-reducing interventions in BRCA mutation carriers</td>
<td>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</td>
<td>Cohort</td>
<td>No RCTs; screening intervals and false-positive calculations varied among studies; some studies lacked within-cohort comparison groups</td>
<td>Consistent</td>
<td>High</td>
<td>Poor</td>
</tr>
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*Continued on following page*
fying 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 ultrasound 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 ultrasound 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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Disclaimer: The findings and conclusions in this review are those of the authors, who are responsible for its content, and do not necessarily represent the views of the AHRQ. No statement in this review should be construed as an official position of the AHRQ or of the U.S. Department of Health and Human Services.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-1684.

Requests for Single Reprints: Heidi D. Nelson, MD, MPH, Pacific Northwest Evidence-based Practice Center, Oregon Health & Science
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