

7.01.09	Risk-Reducing Mastectomy		
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Policy Statement

- I. Risk-reducing mastectomy may be considered **medically necessary** in individuals at high risk of breast cancer. (For definitions of risk levels, see Policy Guidelines section.)
- II. Risk-reducing mastectomy is considered **investigational** for all other indications, including but not limited to contralateral risk-reducing mastectomy in individuals with breast cancer who do not meet high-risk criteria.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

It is strongly recommended that all candidates for risk-reducing mastectomy undergo counseling regarding cancer risks from a health professional other than the operating surgeon skilled to assess cancer risk and to discuss various treatment options, including increased surveillance or chemoprevention with tamoxifen or raloxifene.

There is no standardized method for determining an individual's risk of breast cancer that incorporates all possible risk factors. There are validated risk prediction models, but they are based primarily on family history.

Some known individual risk factors confer a high risk by themselves. The following list includes factors known to indicate a high risk of breast cancer:

- Lobular carcinoma in situ
- A known *BRCA1* or *BRCA2* variant
- Another gene variant associated with high risk, e.g., *TP53* (Li-Fraumeni syndrome), *PTEN* (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), *CDH1*, *STK11*, and *PALB2*
- Received radiotherapy to the chest between 10 and 30 years of age.

A number of other factors may increase the risk of breast cancer but do not by themselves indicate high risk (generally considered to be a lifetime risk of $\geq 20\%$). It is possible that combinations of these factors may be indicative of high risk, but it is not possible to give quantitative estimates of risk. As a result, it may be necessary to individualize the estimate of risk by taking into account numerous risk factors. A number of risk factors, not individually indicating high risk, are included in the National Cancer Institute Breast Cancer Risk Assessment Tool, also called the Gail model.

Another breast cancer risk assessment tool, used in the Women Informed to Screen Depending on Measures of Risk trial, is the Breast Cancer Surveillance Consortium (BCSC) Risk Calculator (<https://tools.bcsc-scc.org/bc5yearrisk/calculator.htm>). The following information is used in that assessment tool:

- History of breast cancer, ductal carcinoma in situ, breast augmentation, or mastectomy
- Age/race/ethnicity
- Number of first-degree relatives (mother, sister, or daughter) diagnosed with breast cancer
- Prior breast biopsies (positive or negative)
- Breast Imaging Reporting and Data System (BI-RADS) breast density (radiologic assessment of breast tissue density by radiologists who interpret mammograms).

Description

Risk-reducing mastectomy is defined as the removal of the breast in the absence of malignant disease to reduce the risk of breast cancer occurrence.

Related Policies

- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2)
- Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Mastectomy is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration.

Rationale

Background

Risk-reducing mastectomy may be considered in women thought to be at high-risk of developing breast cancer, either due to family history, presence of genetic variants (e.g., BRCA1, BRCA2), having received radiotherapy to the chest, or the presence of lesions associated with an increased cancer risk such as lobular carcinoma in situ. Therefore, bilateral risk-reducing mastectomy may be performed to eliminate the risk of cancer arising elsewhere; chemoprevention and close surveillance are alternative risk-reduction strategies. Risk-reducing mastectomies are typically bilateral but can also describe a unilateral mastectomy in a patient who has previously undergone or is currently undergoing a mastectomy in the opposite breast for invasive cancer (i.e., contralateral risk-reducing mastectomy). Use of contralateral risk-reducing mastectomy has increased in the U. S. An analysis of data from the National Cancer Database found that the rate of contralateral risk-reducing mastectomy in women diagnosed with unilateral stage I, II, or III breast cancer increased from approximately 4% in 1998 to 9.4% in 2002.¹

The appropriateness of a risk-reducing mastectomy is a complicated risk-benefit analysis that requires estimates of a patient's risk of breast cancer, typically based on the patient's family history of breast cancer and other factors. Several models are available to assess risks, such as the Claus model and the Gail model. Breast cancer history in first- and second-degree relatives is used to estimate breast cancer risk in the Claus model. The Gail model uses the following five risk factors: age at evaluation, age at menarche, age at first live birth, the number of breast biopsies, and

the number of first-degree relatives with breast cancer. In addition to the patient's risk assessment, the choice of a risk-reducing mastectomy is based on patient tolerance for risk, consideration of changes to appearance and need for additional cosmetic surgery, and the risk-reduction offered by mastectomy vs other options.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Risk-Reducing Mastectomy

Clinical Context and Therapy Purpose

The purpose of a risk-reducing mastectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with a high-risk of breast cancer or extensive mammographic abnormalities precluding excision or biopsy.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals at high-risk of breast cancer or with extensive mammographic abnormalities precluding excision or biopsy. High-risk is generally considered to be a lifetime risk of 20% or greater. The following list of factors may indicate a high-risk of breast cancer:

- lobular carcinoma in situ which is a precursor to invasive lobular cancer (up to 35% may be bilateral)
- a known *BRCA1* or *BRCA2* variant
- another gene variant associated with high-risk, e.g., *TP53* (Li-Fraumeni syndrome), *PTEN* (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), *CDH1*, *STK11*, and *PALB2*
- received radiotherapy to the chest between 10 and 30 years of age.

Interventions

The therapy being considered is a risk-reducing mastectomy.

Risk-reducing mastectomy is defined as the removal of the breast in the absence of malignant disease to reduce the risk of breast cancer occurrence.

Comparators

The following practice is currently being used to treat individuals at high-risk of breast cancer or with extensive mammographic abnormalities precluding excision or biopsy: guideline directed active surveillance or use of chemoprevention.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, functional outcomes, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

This evidence review was informed by a TEC Assessment (1999) that concluded risk-reducing mastectomy met the TEC criteria for patients with a family history of breast cancer.⁵ The Assessment largely focused on a 1999 retrospective cohort analysis that found approximately 13 moderate-risk women would have to have a risk-reducing mastectomy to prevent 1 cancer. For those at high-risk of breast cancer, reduction in breast cancer incidence ranged from 90% to 94%. Four to 8 high-risk women would need to undergo a risk-reducing mastectomy to prevent a single occurrence of breast cancer.

Several recent systematic reviews have evaluated the impact of a risk-reducing mastectomy on health outcomes in women with *BRCA* variants. Li et al (2016) identified 15 controlled studies evaluating the impact of prophylactic surgeries including a bilateral risk-reducing mastectomy on women with *BRCA1* or *BRCA2* variants.⁶ In a meta-analysis of 6 studies with 2555 *BRCA1* or *BRCA2* variant carriers, compared with controls who did not receive a risk-reducing mastectomy, there was a significantly lower risk of subsequent breast cancer in women who had a bilateral risk-reducing mastectomy (relative risk [RR], 0.11; 95% confidence interval [CI], 0.04 to 0.32). However, in a meta-analysis of 2 studies in *BRCA1* or *BRCA2* variant carriers with no history of breast cancer, there was no significant effect on breast cancer-specific mortality (hazard ratio [HR], 0.29; 95% CI, 0.03 to 2.61) or on all-cause mortality (HR, 0.29; 95% CI, 0.03 to 2.61). Similarly, Ludwig et al (2016) identified 10 studies on the incidence of breast cancer after bilateral risk-reducing mastectomy in *BRCA1* or *BRCA2* carriers and found a significant reduction in breast cancer risk ranging from 89.5% to 100%.⁷ These reviewers did not conduct pooled analyses of studies on the impact of a risk-reducing mastectomy on mortality.

Honold and Camus (2018) extracted data from systematic reviews and primary studies to determine if risk-reducing mastectomy for women with *BRCA* genes is more effective than active surveillance (periodic clinical examination plus imaging tests) at preventing breast cancer.⁸ The authors analyzed data from 13 systematic reviews with a total of 50 studies. The results suggest with high certainty of evidence (based on GRADE system) that active surveillance is less effective at preventing breast

cancer than risk-reducing mastectomy, with 254 per 1000 patients developing breast cancer with only active surveillance and 12 per 1000 with risk-reducing mastectomy (risk ratio, 0.05; 95% CI, 0.02 to 0.1). Mortality from any cause was also higher for active surveillance than for risk-reducing mastectomy (risk ratio, 0.12; 95% CI, 0.04 to 0.36). The authors also concluded with moderate evidence that up to 64% of women who received the surgery experienced adverse effects (e.g., lower sensitivity, pain, infection, edema, contracture). In addition, they found low certainty of evidence that those who underwent risk-reducing mastectomy had a decrease in anxiety and depressive symptoms, did not regret having the surgery, and were satisfied with the cosmetic results. The results of this meta-analysis do not apply to individuals with low to moderate risk of breast cancer. A Cochrane review by Carbine et al (2018) examined the impact of risk-reducing mastectomy on mortality and other health outcomes.⁹ Reviewers did not identify any RCTs. Sixty-one observational studies with some methodologic limitations were identified. The studies presented data on 15,077 individuals with a wide range of risk factors for breast cancer who underwent a risk-reducing mastectomy. Studies on the incidence of breast cancer and/or disease-specific mortality (n=21) reported reductions in both after a bilateral risk-reducing mastectomy, particularly for those with *BRCA1* or *BRCA2* variants.

Section Summary: Risk-Reducing Mastectomy

Evidence from systematic reviews has found that risk-reducing mastectomy reduces the incidence of breast cancer in women at high-risk of breast cancer, especially those with *BRCA1*, *BRCA2*, and other pathogenic variants, and those with a formal high-risk familial risk assessment. In addition, 1 study reported that risk-reducing mastectomy could be associated with high satisfaction levels. Fewer studies have examined the impact of a risk-reducing mastectomy on overall or breast cancer-specific survival.

Contralateral Risk-Reducing Mastectomy

Clinical Context and Therapy Purpose

The purpose of a contralateral risk-reducing mastectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with unilateral breast cancer who are not otherwise at high-risk.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with unilateral breast cancer who are not otherwise at high-risk.

Interventions

The therapy being considered is a contralateral risk-reducing mastectomy.

Comparators

The following practice is currently being used to treat individuals with unilateral breast cancer who are not otherwise at high risk: active surveillance with clinical examination, imaging studies, and guideline-based treatment of primary breast cancer.

Outcomes

The general outcomes of interest are OS, disease-specific survival, functional outcomes, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Incidence of a Second Primary Breast Cancer

The potential for a contralateral risk-reducing mastectomy to impact survival is related to its association with a reduced risk of subsequent primary breast cancer in the other breast (ie, contralateral breast cancer [CBC]). In general, according to data from the U.S. Surveillance, Epidemiology and End Results (SEER) database, annual rates of CBC were stable between 1975 and 1985, after which rates declined about 3% per year (95% CI, 2.7% to 3.5%).¹⁰ Beginning in 1990, the annual decline in CBC rates was only in individuals with estrogen receptor-positive cancer, with no decrease in individuals with estrogen receptor-negative cancer. The investigators suggested that the decrease in CBC rates after estrogen receptor-positive cancer might be attributed at least in part to the increased availability of adjuvant hormone therapies.

Studies were sought to assess the risk of CBC in women who met high-risk and average-risk criteria. Molina-Montes et al (2014) published a systematic review of studies on the risk of second primary breast cancer in women with and without *BRCA1* or *BRCA2* variants.¹¹ Twenty studies were included (12 retrospective cohort studies, 2 prospective cohort studies, 6 case-control studies). Most studies included only individuals who had undergone genetic testing; it is likely that even those who tested negative had other risk factors that motivated testing. A meta-analysis found that the cumulative risk of second primary breast cancer at 5 years after the initial diagnosis was 14% (95% CI, 9% to 19%) in *BRCA1* or *BRCA2* variant carriers and 3% (95% CI, 2% to 5%) in noncarriers. The cumulative risk of a second primary cancer at 10 years after the initial diagnosis was 22% (95% CI, 18% to 27%) in *BRCA1* or *BRCA2* variants and 5% (95% CI, 3% to 7%) in noncarriers.

Survival After Contralateral Risk-Reducing Mastectomy

As is the case for bilateral risk-reducing mastectomy, no RCTs evaluating the effect of contralateral risk-reducing mastectomy on health outcomes have been published. There are a number of observational studies, including some with large sample sizes, and systematic reviews of those observational studies. Observational studies have attempted to control for potential confounders, but not all relevant factors were measured, and the possibility of selection bias remains.

Systematic Reviews

The previously summarized Cochrane review by Carbine et al (2018) also assessed various outcomes, including mortality and disease-free survival, among individuals who received a contralateral risk-reducing mastectomy.⁹ Twenty-six observational studies assessed outcomes in individuals who received contralateral risk-reducing mastectomy. While results showed a reduced incidence of CBC among those who received a contralateral risk-reducing mastectomy, results on disease-specific mortality were inconsistent. Seven of the included studies showed no survival advantage. One additional study showed an improvement in all-cause mortality associated with contralateral risk-reducing mastectomy; however, significance was lost after adjustment for bilateral risk-reducing salpingo-oophorectomy. The authors attributed the variability in mortality findings, in part, to selection bias, since younger, healthier individuals may be more likely to opt for contralateral risk-reducing mastectomy.

A systematic review and meta-analysis of studies on contralateral risk-reducing mastectomy were published by Fayanju et al (2014).¹² The authors conducted a literature search through March 2012 and identified 17 observational studies that compared the incidence of CBC in individuals with unilateral disease who did and did not undergo a contralateral risk-reducing mastectomy. Fourteen of the 17 studies were included in various meta-analyses. In a meta-analysis of 4 studies, mortality

from breast cancer was lower in the group that had a contralateral risk-reducing mastectomy (RR, 0.69; 95% CI, 0.56 to 0.85). Moreover, in a meta-analysis of data from 6 studies, OS was significantly higher in patients who underwent a contralateral risk-reducing mastectomy (n=10,666) than those who did not (n=145,490; RR, 1.09; 95% CI, 1.06 to 1.11). Reviewers also conducted a subgroup analysis by risk level. A meta-analysis of patients considered high-risk, which included *BRCA* variant carriers and/or those with a family history of breast cancer (4 studies, 616 undergoing contralateral risk-reducing mastectomy, 1318 not undergoing contralateral risk-reducing mastectomy) found that neither OS nor mortality from breast cancer differed significantly among individuals who had or did not have a contralateral risk-reducing mastectomy. The RR of breast cancer mortality with and without a contralateral risk-reducing mastectomy was 0.66 (95% CI, 0.27 to 1.64). For OS with and without a contralateral risk-reducing mastectomy, the RR was 1.09 (95% CI, 0.97 to 1.24). The absolute risk-reduction for metachronous breast cancer did not differ between individuals with and without a contralateral risk-reducing mastectomy when data from all 8 studies were analyzed (risk difference, -18.0%; 95% CI, -42.0% to 5.9%), but was significantly lower in those with a contralateral risk-reducing mastectomy in the 4 studies exclusively enrolling individuals at increased familial/genetic risk (risk difference, -24.0%; 95% CI, -35.6% to -12.4%). Commenting on the totality of findings, reviewers stated that the improvement in survival after a contralateral risk-reducing mastectomy in the general breast cancer population was likely not due to a decreased incidence of CBC, but rather was secondary to selection bias (e.g., contralateral risk-reducing mastectomy recipients may be otherwise healthier and have better access to health care).

Observational Studies

Studies in the Fayanju et al (2014) systematic review were published between 1997 and 2005. More recent large observational studies, described below, reported mixed results for OS and disease-specific survival.

An analysis of 17 years of SEER data from 245,418 women in California with unilateral breast cancer assessed secondary contralateral cancer incidence and mortality in women who had bilateral mastectomy or breast conserving therapy.¹³ The study adjusted for numerous potential confounders, including demographic and socioeconomic characteristics, clinical characteristics and disease state, and year of diagnosis. Patient race/ethnicity was mostly White (65.1%), followed by Hispanic (15.9%) and Black (5.4%). After a median 7 years follow-up, the study found that when compared with breast conserving therapy that included radiotherapy, bilateral mastectomy was associated with a reduced risk of secondary breast cancer (HR, 0.11; 95% CI, 0.07 to 0.14) while unilateral mastectomy was associated with increased risk (HR, 1.07; 95% CI, 1.02 to 1.13). However, the study also found bilateral mastectomy was not associated with a significant reduction in breast cancer-related mortality relative to breast-conserving therapy (HR, 1.03; 95% CI, 0.96 to 1.11). Compared to White patients, Black (HR, 1.23; 95% CI, 1.13 to 1.35) and Filipina (HR, 1.30; 95% CI, 1.17 to 1.44) individuals had a higher risk of second contralateral breast cancer. Compared to White patients, Black patients had an increased risk of breast cancer death (HR, 1.21; 95% CI, 1.14 to 1.28) while individuals of all other races had a reduced risk of death.

Wong et al (2017) evaluated 496,488 individuals diagnosed with unilateral invasive breast disease.¹⁴ Within this cohort, 58.6% (n=295,860) underwent breast-conserving surgery, 33.4% (n=165,888) had a unilateral mastectomy, and 7% (n=34,740) had a contralateral risk-reducing mastectomy. The median age was 50 years in the contralateral risk-reducing mastectomy group and 60 years in the breast conservation group (p<.001). Patient race/ethnicity was mostly White (73.3%), followed by Black (9.5%), Hispanic (8.7%), and Asian/Pacific Islander (7.5%). Patients were followed for a median of 8.25 years. In an analysis adjusting for age and other factors including the stage of the disease, OS was significantly higher after breast conservation than after a contralateral risk-reducing mastectomy (HR, 1.08; 95% CI, 1.03 to 1.14). Similarly, breast cancer-specific survival was significantly higher in the breast conservation group than in the contralateral risk-reducing mastectomy group (HR, 1.08; 95% CI, 1.01 to 1.16).

An analysis of SEER data by Kruper et al (2014) suggested the association between contralateral risk-reducing mastectomy and reduced mortality identified in some data analyses could be attributed at least in part to the selection of a healthier cohort of women for contralateral risk-reducing mastectomy.¹⁵ In the case-control analysis including 28,015 contralateral risk-reducing mastectomy patients and 28,015 unilateral mastectomy patients in the SEER database, patients were matched by age group, race/ethnicity, extent of surgery, tumor grade, tumor classification, node classification, estrogen receptor status, and propensity score. The investigators were unable to match for *BRCA* or another genetic variant status. Patient race/ethnicity was mostly White (83%), followed by Hispanic (7%), Black (6%), and Asian/Pacific Islander (5%). When all matched patients were included, disease-specific survival and OS were significantly lower in individuals who underwent unilateral mastectomy compared with contralateral risk-reducing mastectomy. For disease-specific survival, the HR was 0.83 (95% CI, 0.77 to 0.90); for OS, it was 0.77 (95% CI, 0.73 to 0.82). Presumably, a contralateral risk-reducing mastectomy would increase survival by lowering the risk of CBC. The authors conducted another analysis excluding individuals diagnosed with CBC; the remaining sample was still large (25,924 individuals with unilateral mastectomy, 26,299 individuals with contralateral risk-reducing mastectomy). In the analysis excluding those with CBC, disease-specific survival, and OS remained significantly lower in individuals who had unilateral versus contralateral risk-reducing mastectomy.

For disease-specific survival, the HR was 0.87 (95% CI, 0.80 to 0.94); for OS, it was 0.76 (95% CI, 0.71 to 0.81). The investigators suggested that the survival benefits found in CBC patients were not due to prevention of CBC but to selection bias (e.g., healthier individuals choosing CBC). A multivariate analysis showed that Black and Hispanic patients had increased risk of OS compared to White patients (HR, 1.63; 95% CI, 1.45 to 1.82 and HR, 1.21, 95% CI, 1.07 to 1.38, respectively). A limitation of the analysis was the inability to control for risk factors including gene variant status, family history, and a history of radiotherapy to the chest between ages 10 and 30 years.

Yao et al (2013) evaluated OS after contralateral risk-reducing mastectomy using data from the National Cancer Data Base.¹ The database collects information from 1450 Commission on Cancer-accredited cancer programs. The analysis included 219,983 individuals who had a mastectomy for unilateral breast cancer; 14,994 (7%) of these individuals underwent a contralateral risk-reducing mastectomy at the time of their mastectomy surgery. The investigators did not report risk factors such as known genetic variants. Patient race/ethnicity was mostly White (83.9%), followed by Black (8.9%), Hispanic (3.6%), and Asian/Pacific Islander (2.2%). The 5-year OS rate was 80%. In an analysis adjusting for confounding factors, the risk of death was significantly lower in patients who had a contralateral risk-reducing mastectomy than in those who did not. The adjusted HR for OS was 0.88 (95% CI, 0.83 to 0.93). The absolute risk of death over 5 years with contralateral risk-reducing mastectomy was 2.0% lower than without. In subgroup analyses, there was a survival benefit after contralateral risk-reducing mastectomy for individuals 18 to 49 years and 50 to 69 years but not for those 70 years or older. There was also a survival benefit for individuals with stage I and II tumors but not stage III tumors. Compared to White patients, Black patients had decreased survival (HR, 1.32; 95% CI, 1.27 to 1.37) while individuals of all other races had improved survival.

In a subsequent study, Pesce et al (2014) focused on a subgroup of patients who were young (<45 years old) with stage I or II breast cancer.¹⁶ A total of 4338 (29.7%) of 14,627 individuals in this subgroup had a contralateral risk-reducing mastectomy. Patient race/ethnicity was mostly White (76.5%), followed by Black (10.9%), Hispanic (7.6%), and Asian/Pacific Islander (4.4%). Median follow-up was 6.1 years. In a multivariate analysis controlling for potentially confounding factors, OS did not differ significantly between patients who underwent a unilateral mastectomy and those who also had a contralateral mastectomy (HR, 0.93; 95% CI, 0.79 to 1.09). Moreover, among individuals younger than 45 years with estrogen receptor-negative cancer, there was no significant improvement in OS in those who had a contralateral risk-reducing mastectomy or a unilateral mastectomy (HR, 1.13; 95% CI, 0.90 to 1.42). Compared to White patients, Black patients had decreased OS (HR, 1.48; 95% CI, 1.24 to 1.78). Among other races, OS was similar to White patients.

Yang et al (2021) conducted an analysis of SEER data from 1998 to 2016 of 5118 men with unilateral breast cancer who underwent contralateral risk-reducing mastectomy (n=209 [4.1%]).¹⁷ Patient race/ethnicity was mostly White (82.3%), followed by Black (12.4%), and other races (4.8%). In 1998, contralateral risk-reducing mastectomy was undertaken in 1.7% of men compared to 6.3% in 2016 ($p < .0001$). Compared to unilateral mastectomy, contralateral risk-reducing mastectomy improved OS (HR, 0.58; 95% CI, 0.37 to 0.89) but a survival benefit was not seen after propensity score-matching (HR, 0.83; 95% CI, 0.46 to 1.52). Contralateral risk-reducing mastectomy did not improve disease-specific survival compared to unilateral mastectomy.

Adverse Events

There are risks and benefits associated with contralateral risk-reducing mastectomy. In particular, several analyses have found higher rates of surgical complications in individuals undergoing contralateral risk-reducing mastectomy (bilateral mastectomy) compared with those undergoing unilateral mastectomy. Besides morbidity associated with these complications, surgical complications may delay receiving adjuvant therapy.

Murphy et al (2021) published a systematic review and meta-analysis evaluating the complications associated with contralateral risk-reducing mastectomy.¹⁸ Fifteen cohort studies (14 retrospective; 1 prospective) were included (N=6,583). Definitions of what constituted as a complication varied amongst the included studies. In patients who underwent unilateral plus contralateral prophylactic mastectomy, the diseased breast was significantly more susceptible to complications compared to the contralateral breast (RR, 1.24; $p = .03$). Studies that were stratified by reconstructive method reported that complication risk was significantly higher for unilateral plus contralateral prophylactic mastectomy compared to unilateral mastectomy alone in patients with no reconstruction (RR, 2.03; $p = .0003$), autologous reconstruction (RR, 1.32; $p = .005$), and prosthetic-based reconstruction (RR, 1.42; $p = .003$).

Schroeder et al (2020) conducted a population-based study of 12959 women who underwent unilateral mastectomy or contralateral risk-reducing mastectomy using data from the New York Statewide Planning and Research Cooperative System.¹⁹ Of these, 1384 underwent a contralateral risk-reducing mastectomy and 11,575 underwent a unilateral mastectomy. After controlling for confounding factors (ie, race, ethnicity, year of operation, and type of insurance) and stratifying by breast reconstruction, no difference was found in the likelihood of complications or additional breast-related procedures needed between women who received contralateral risk-reducing mastectomy and those who received unilateral mastectomy (both without breast reconstruction). Addition of breast reconstruction was associated with significant increases in complications and breast-related procedures, both in women with unilateral mastectomy (odds ratio [OR], 3.6; $p < .001$ and OR, 13.7; $p < .001$, respectively) and in those with contralateral risk-reducing mastectomy (OR, 3.3; $p < .001$ and OR, 30.1; $p < .001$, respectively). Patients who underwent contralateral risk-reducing mastectomy were also significantly more likely to undergo breast reconstruction compared to those who underwent unilateral mastectomy (93.1% vs. 46.3%; $p < .001$).

Silva et al (2015) published a large multicenter study including 20,501 women with unilateral breast cancer from the American College of Surgeons National Surgery Quality Improvement Program database.²⁰ A total of 13,268 (64.7%) women underwent a unilateral mastectomy, and 7233 (35.3%) had a bilateral mastectomy. The analysis did not report on high-risk factors such as *BRCA* variant status or family history. All women had breast reconstruction; a higher proportion of women who had a unilateral mastectomy (19.5%) than bilateral mastectomy (8.9%) had autologous reconstruction; the remainder had implant-based reconstruction. The authors conducted analyses controlling for confounding variables (ie, age, race, smoking, diabetes, chronic pulmonary disease, hypertension) and stratifying by type of implant. The rate of overall complications was significantly higher for women who had a bilateral mastectomy, regardless of reconstruction type. Among women with implant reconstructions, overall complication rates were 10.1% after a bilateral mastectomy and 8.8% after a unilateral mastectomy (adjusted OR, 1.20; 95% CI, 1.08 to 1.33). In women with autologous

reconstructions, overall complication rates were 21.2% after a bilateral mastectomy and 14.7% after a unilateral mastectomy (adjusted OR, 1.60; 95% CI, 1.28 to 1.99). The most common complication was reoperation within 30 days, followed by surgical site complications. Transfusion rates were also significantly higher ($p < .001$) in women with bilateral mastectomies who had either type of reconstruction. The rates of medical complications were relatively low—approximately 1% of women who had implant reconstructions and 3% of women who had autologous reconstructions experienced a medical complication (ie, pneumonia, renal insufficiency or failure, sepsis, urinary tract infection, venous thromboembolism)—and did not differ significantly between unilateral and bilateral mastectomies.

Several single-center studies have also reported significantly higher surgical complication rates after bilateral compared with unilateral mastectomy. For example, in a study by Miller et al (2013), which included 600 women with unilateral breast cancer, contralateral risk-reducing mastectomy remained associated with a significantly higher risk of any complication (OR, 1.53; 95% CI, 1.04 to 2.25) and a significantly higher risk of major complications (OR, 2.66; 95% CI, 1.37 to 5.19) compared with unilateral mastectomy.²¹ Moreover, in a study by Eck et al (2014), which assessed 352 women with unilateral breast cancer, 94 (27%) women had complications, 48 (14%) in the unilateral mastectomy group, and 46 (13%) in the bilateral mastectomy group.²² The difference between groups was not statistically significant ($p = .11$) but this study might have been underpowered. Eck et al (2014) found a significant delay in adjuvant therapy after surgical complications: women with complications waited longer before receiving adjuvant therapy than those without complications (49 days vs. 40 days, $p < .001$).

Section Summary: Contralateral Risk-Reducing Mastectomy

Large observational studies have reported inconsistent findings on the survival benefit of contralateral risk-reducing mastectomy in women with unilateral breast cancer who do not otherwise meet high-risk criteria. Researchers have suggested that improvements in survival after contralateral risk-reducing mastectomy in the general breast cancer population found in some studies are due at least in part to selection bias. Moreover, there are risks of complications associated with both the surgical and reconstruction procedures.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2016 Input

In response to requests, input was received from 1 specialty society and 6 academic medical centers while this policy was under review in 2016. Input addressed the use of contralateral prophylactic (risk-reducing) mastectomy in women with unilateral breast cancer who are not otherwise at high-risk for developing breast cancer in the contralateral breast. The input was mixed. Clinicians offered suggestions for modifying high-risk criteria but there was no consensus on potential additional risk factors.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to

guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Genetics and Genomics

In 2021, the American College of Genetics and Genomics published a guideline on management of individuals with *PALB2* variants, which recommends that risk-reducing mastectomy be considered as an option based on personal risk.²³

American Society for Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology

In 2020, the American Society for Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology published joint guidelines on management of hereditary breast cancer.²⁴ The guideline discusses management of patients with breast cancer with germline mutations in breast cancer susceptibility genes (e.g., *BRCA1/2*, *ATM*, *TP53*) and makes the following recommendations regarding risk-reducing mastectomy:

"Surgical management of the index malignancy (...contralateral risk-reducing mastectomy [CRRM]) in *BRCA1/2* mutation carriers should be discussed, considering the increased risk of CBC [contralateral breast cancer] and possible increased risk of an ipsilateral new primary breast cancer compared with noncarriers (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: strong)."

"For women with breast cancer who have a *BRCA1/2* mutation and who have been treated or are being treated with unilateral mastectomy, CRRM should be offered. CRRM is associated with a decreased risk of CBC; there is insufficient evidence for improved survival."

"Decisions regarding risk-reducing mastectomy (bilateral or contralateral) are highly personal and must be individualized for every patient. Studies show that women who opt for prophylactic mastectomy report positive outcomes, including decreased concern about developing breast cancer. This benefit must be weighed against possible problems with implants or reconstructive therapy and potential adverse feelings related to body image, femininity, and sexuality. Most patients who opt for prophylactic mastectomy demonstrate satisfaction with their decision."

"For women with breast cancer who have a mutation in a moderate-penetrance breast cancer predisposition gene and who have been treated or are being treated with unilateral mastectomy, the decision regarding CRRM should not be based predominantly on mutation status. Additional factors that predict CBC such as age at diagnosis and family history should be considered, as they are in all cases. The impact of CRRM on decreasing risk of CBC is dependent on the risk of CBC for each individual gene. Data regarding the risk of CBC resulting from moderate-penetrance genes are limited (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate)." The guideline also provides recommendations for assessing the risk of CBC and role of risk-reducing mastectomy in *BRCA1/2* mutation carriers (Evidence quality: low; Strength of recommendation: moderate) and in women with breast cancer who have a *BRCA1/2* mutation who have been treated or are being treated with unilateral mastectomy when considering contralateral risk-reducing mastectomy (Evidence quality: intermediate; Strength of recommendation: moderate). The guideline recommends consideration of the following:

- Age at diagnosis (the strongest predictor of future CBC)
- Family history of breast cancer
- Overall prognosis from this or other cancers (e.g., ovarian)
- Ability of patient to undergo appropriate breast surveillance (magnetic resonance imaging [MRI])
- Comorbidities
- Life expectancy.

American Society of Breast Surgeons

In 2016, a consensus statement from the American Society of Breast Surgeons made the following recommendations on contralateral risk-reducing mastectomy²⁵:

"CPM [contralateral prophylactic mastectomy] should be considered for those at significant risk of CBC [contralateral breast cancer]

- Documented *BRCA1/2* carrier
- Strong family history, but patient has not undergone genetic testing
- History of mantle chest radiation before age 30 years.

CPM can be considered for those at lower risk of CBC

- Gene carrier of... *CHEK-2, PALB2, p53, CDH1*
- Strong family history, patient *BRCA* negative, no known *BRCA* family member.

CPM may be considered for other reasons

- To limit contralateral breast surveillance (dense breasts, failed surveillance, recall fatigue)
- To improve reconstructed breast symmetry
- To manage risk aversion ... [or] extreme anxiety." (note: anxiety may be better managed through psychological support strategies.)

CPM should be discouraged

- Average-risk women with unilateral breast cancer
- Women with advanced index cancer
- Women at high risk for surgical complications (e.g.,...comorbidities, obesity, smoker, diabetes)
- *BRCA* negative with a family of *BRCA*-positive carriers
- Male breast cancer, including *BRCA* carriers.

National Cancer Institute

In 2013, the National Cancer Institute updated its fact sheet on risk-reducing surgery for breast cancer.²⁶ The fact sheet stated women with the following characteristics may consider bilateral risk-reducing mastectomy:

- Deleterious variant in *BRCA1* or *BRCA2*
- Strong family history of breast cancer
- Lobular carcinoma in situ and family history of breast cancer
- Radiotherapy to the chest before the age of 50 years.

Considering contralateral risk-reducing mastectomy, the Institute stated: "Given that most women with breast cancer have a low risk of developing the disease in their contralateral breast, women who are not known to be at a very high risk but who remain concerned about cancer development in their other breast may want to consider options other than surgery to further reduce their risk of a contralateral breast cancer."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) has made recommendations on several cancers relevant to this evidence review. On breast cancer risk-reduction (v. 1.2023), the NCCN recommends:

"Risk-reducing mastectomy should generally be considered only in women with a pathogenic/likely pathogenic genetic mutation (not variants of undetermined significance) conferring a high risk for breast cancer..., compelling family history, or possibly with prior thoracic RT [radiation therapy] at <30 years of age. The value of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic mutations in other genes associated with a 2-fold or greater risk for breast cancer ... in the absence of a compelling family history of breast cancer is unknown."²⁷

For invasive breast cancer (v. 4.2023) the NCCN has discouraged contralateral risk-reducing mastectomy, except for certain high-risk situations (noted in the risk-reduction guideline previously discussed).²⁸ The guidelines state:

"...risk reduction mastectomy of a breast contralateral to a known unilateral breast cancer treated with mastectomy or breast-conserving therapy is discouraged by the panel. "

As part of a genetic/familial high-risk assessment for breast, ovarian, and pancreatic cancer (v. 3.2023), the NCCN recommends that the option of risk-reduction mastectomy be discussed in women with *BRCA*-related breast and/or ovarian syndrome, Li-Fraumeni syndrome, and Cowden syndrome or *PTEN* hamartoma tumor syndrome.²⁹ In addition, the NCCN guidelines recommend that risk-reducing mastectomy be considered based on family history in women with certain genetic variants including *ATM*, *NF1*, *STK11*, *PALB2*, *CHEK2*, and *CDH1*.

Society of Surgical Oncology

In 2017, the Society of Surgical Oncology updated its position statement on risk-reducing mastectomy.³⁰ The position statement concluded the following about risk-reducing mastectomy:

"There is no single-risk threshold above which risk-reducing mastectomy is clearly indicated, and it is important for treating physicians and surgeons to explain to individuals not only the risk assessment but also all available treatment strategies to facilitate a shared decision-making process."

"The available data suggest that BMP [bilateral prophylactic mastectomy] confers a survival advantage in women with the highest risk who undergo the procedure at a relatively early age ... the impact of CPM [contralateral prophylactic mastectomy] in women with invasive breast cancer is more difficult to assess ... however, CPM does not appear to confer a survival advantage."

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for prophylactic mastectomy have been identified.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in June 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
- High-risk of breast cancers
- Familial history as it relates to high-risk breast cancer
- Previous radiotherapy to the chest

Post Service (in addition to the above, please include the following):

- Operative report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	19303	Mastectomy, simple, complete
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/31/2015	BCBSA Medical Policy adoption
04/01/2016	Policy revision without position change
09/01/2017	Policy revision without position change
07/01/2018	Policy statement clarification
09/01/2018	Policy title change from Prophylactic Mastectomy Policy revision without position change
10/01/2019	Policy revision without position change
09/01/2023	Policy reactivated. Previously archived from 10/01/2020 to 08/31/2023.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue

Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	AFTER <i>Blue font: Verbiage Changes/Additions</i>
<p>Reactivated Policy</p> <p>Policy Statement: N/A</p>	<p>Risk-Reducing Mastectomy 7.01.09</p> <p>Policy Statement:</p> <ul style="list-style-type: none"> I. Risk-reducing mastectomy may be considered medically necessary in individuals at high risk of breast cancer. (For definitions of risk levels, see Policy Guidelines section.) II. Risk-reducing mastectomy is considered investigational for all other indications, including but not limited to contralateral risk-reducing mastectomy in individuals with breast cancer who do not meet high-risk criteria.