7.01.09  Risk-Reducing Mastectomy

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Policy Statement

Risk-reducing mastectomy may be considered medically necessary in patients at high risk of breast cancer. (For definitions of risk levels, see Policy Guidelines section.)

Risk-reducing mastectomy may be considered medically necessary in patients with such extensive mammographic abnormalities (i.e., calcifications) that adequate biopsy or excision is impossible.

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.

Policy Guidelines

It is strongly recommended that all candidates for risk-reducing mastectomy undergo counseling regarding cancer risks from a health professional skilled other than the operating surgeon 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 a woman’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, and STK11
- 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 greater than or equal to 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. 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)
- BI-RADS breast density (radiologic assessment of breast tissue density by radiologists who interpret mammograms)
Another breast cancer risk assessment tool is the IBIS Breast Cancer Risk Evaluation Tool (http://www.ems-trials.org/riskevaluator/). It uses the information above along with:

- Age of menarche
- Height, weight
- Age of first child or if nulliparous
- Menopausal state (pre, post or peri) and age at menopause

**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**

- 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

**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...
Risk-Reducing Mastectomy

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, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one 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. RCTs 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.

Risk-Reducing Mastectomy
Clinical Context and Therapy Purpose
The purpose of risk-reducing mastectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with a high-risk of breast cancer or extensive mammographic abnormalities precluding excision or biopsy.

The question addressed in this evidence review is: Does risk-reducing mastectomy improve the net health outcome in individuals at high-risk for breast cancer?

The following PICO's were used to select literature to inform this review.

Patients
The relevant population of interest are women at high-risk of breast cancer or 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, and STK11,
• 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.

Risk-reducing mastectomy is performed by a surgical oncologist in an inpatient clinical setting.

Comparators
Comparators of interest include guideline directed active surveillance or use of chemoprevention.

Active surveillance and prescription of chemoprevention are performed by oncologists, primary care providers in an outpatient clinical setting.

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:

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

Systematic Reviews
This evidence review was informed by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (1999) that concluded risk-reducing mastectomy met the TEC criteria for patients with a family history of breast cancer.\(^2\) 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 eight high-risk women would need to undergo a risk-reducing mastectomy to prevent a single occurrence of breast cancer.

A Cochrane review by Lostumbo et al (2010) examined the impact of risk-reducing mastectomy on mortality and other health outcomes.\(^3\) Reviewers did not identify any RCTs. Thirty-nine observational studies with some methodologic limitations were identified. The studies presented data on 7384 women 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 reported reductions after a bilateral risk-reducing mastectomy, particularly for those with BRCA1 or BRCA2 variants. Reviewers concluded that, while the available observational data suggested bilateral risk-reducing mastectomy reduced the rate of breast cancer mortality, more rigorous studies (ideally RCTs) were needed, and that bilateral risk-reducing mastectomy should only be considered for patients at very high-risk of disease.
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. 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%. These reviewers did not conduct pooled analyses of studies on the impact of a risk-reducing mastectomy on mortality.

For their meta-analysis, 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. 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 [RR]=0.05; 95% CI: 0.02 to 0.1). Mortality from any cause was also higher for active surveillance than for risk-reducing mastectomy (RR=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 women with low to moderate risk of breast cancer.

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, one 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 contralateral risk-reducing mastectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with unilateral breast cancer but are not otherwise at high-risk.

The question addressed in this evidence review is: Does contralateral risk-reducing mastectomy improve the net health outcome in individuals with unilateral breast cancer who are otherwise not at high-risk for breast cancer recurrence?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with unilateral breast cancer but are not otherwise at high-risk.
Interventions
The therapy being considered is a contralateral risk-reducing mastectomy. Contralateral risk-reducing mastectomy is performed by a surgical oncologist in an inpatient clinical setting.

Comparators
Comparators of interest include 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.

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 (i.e., 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%). Beginning in 1990, the annual decline in CBC rates was only in women with estrogen receptor-positive cancer, with no decrease in women 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. Twenty studies were included (12 retrospective cohort studies, 2 prospective cohort studies, 6 case-control studies). Most studies included only women 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 a systematic review 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.

A systematic review and meta-analysis of studies on contralateral risk-reducing mastectomy were published by Fayanju et al (2014). They conducted a literature search through March 2012 and identified 17 observational studies that compared the incidence of CBC in women 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=10666) than those did not (n=145490; 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 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 women 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 women 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 women with a contralateral risk-reducing mastectomy in
the 4 studies exclusively enrolling women 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).

More recent large observational analyses are described below, several of which analyzed data
from the SEER database.

Wong et al (2017) evaluated 496488 women diagnosed with unilateral invasive breast
disease. Within this cohort, 58.6% (n=295860) underwent breast-conserving surgery, 33.4%
(n=165888) had a unilateral mastectomy, and 7% (n=34740) 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<0.001). 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. In the case-control analysis including 28015 contralateral risk-
reducing mastectomy patients and 28015 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. When all
matched patients were included, disease-specific survival (DSS) and OS were significantly lower
in women who underwent unilateral mastectomy compared with contralateral risk-reducing
mastectomy. For DSS, 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 women diagnosed with CBC;
the remaining sample was still large (25924 women with unilateral mastectomy, 26299 women
with contralateral risk-reducing mastectomy). In the analysis excluding women with CBC, DSS,
and OS remained significantly lower in women who had unilateral vs contralateral risk-
patients were reducing mastectomy. For DSS, 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 not due
to prevention of CBC but to selection bias (e.g., healthier women choosing CBC). 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. The database collects information from 1450 Commission on
Cancer-accredited cancer programs. The analysis included 219983 women who had
a mastectomy for unilateral breast cancer; 14,994 (7%) of these women 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. The 5-year OS rate was 80%. In an analysis adjusting for confounding factors, the risk of death was significantly lower in women who had a contralateral risk-reducing mastectomy than in women who did not. The adjusted HR for OS was 0.88 (95% CI, 0.83 to 0.93). The absolute risk of death over five 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 women with stage I and II tumors but not stage III tumors.

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. A total of 4,338 (29.7%) of 14,627 women in this subgroup had a contralateral risk-reducing mastectomy. 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 women 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).

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 women undergoing contralateral risk-reducing mastectomy (bilateral mastectomy) compared with women undergoing a unilateral mastectomy. Besides morbidity associated with these complications, surgical complications may delay receiving adjuvant therapy.

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. A total of 13,268 (64.7%) women underwent a unilateral mastectomy, and 7,233 (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 (i.e., 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 odds ratio [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<0.001) 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 (i.e., 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. 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. The difference between groups was not statistically significant (p=0.11) 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 < 0.001).

Section Summary: Contralateral Prophylactic 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.

Summary of Evidence

For individuals who have a high-risk of breast cancer or extensive mammographic abnormalities precluding excision or biopsy who receive a risk-reducing mastectomy, the evidence includes systematic reviews and observational studies. The relevant outcomes are OS, disease-specific survival, functional outcomes, and treatment-related morbidity. Studies have found that a risk-reducing mastectomy lowers subsequent breast cancer incidence and increases survival in select high-risk patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unilateral breast cancer but are not otherwise at high-risk who receive a contralateral risk-reducing mastectomy, the evidence includes systematic reviews and observational studies. The relevant outcomes are OS, disease-specific survival, functional outcomes, and treatment-related morbidity. Available studies do not demonstrate a consistent survival benefit in women without high-risk criteria. Moreover, there are risks associated with a contralateral risk-reducing mastectomy for both the primary surgical and reconstruction procedures. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

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.

In response to requests from Blue Cross Blue Shield Association, input was received from 1 specialty society and 6 academic medical centers 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

Society of Surgical Oncology

The Society of Surgical Oncology (2017) updated its position statement on risk-reducing mastectomy. 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."

National Cancer Institute
The National Cancer Institute (2013) updated its fact sheet on risk-reducing surgery for breast cancer. 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 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 their risk of a contralateral breast cancer."

American Society of Breast Surgeons
A consensus statement from the American Society of Breast Surgeons (2016) made the following recommendations on contralateral risk-reducing mastectomy:

"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 breast symmetry in reconstruction.
- To manage risk aversion ... [or] extreme anxiety." (note: anxiety may better be measured through psychological support.)

CPM should be discouraged
- Average-risk women with unilateral breast cancer.
- Women with advanced stage index cancer....
- Women at high risk of surgical complications (e.g., comorbidities, obesity, smoking, diabetes).
- ...BRCA negative with a family of BRCA-positive carriers.
- "Males with breast cancer, including BRCA carriers."

National Comprehensive Cancer Network
The NCCN has made recommendations on several cancers relevant to this evidence review. On breast cancer risk-reduction (v.1.2019), the NCCN recommends:

"Risk-reducing mastectomy should generally be considered only in women with a genetic mutation conferring a high risk for breast cancer..., compelling family history, or possibly with LCIS [lobular carcinoma in situ] or prior thoracic radiation therapy at <30 years of age.... The value of risk-reducing mastectomy in women with deleterious 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."19.

For invasive breast cancer (v.1.2019) the NCCN has discouraged contralateral risk-reducing mastectomy, except for certain high-risk situations (noted in the risk-reduction guideline previously discussed).20. The guidelines state: "The small benefits from contralateral prophylactic mastectomy for women with unilateral breast cancer must be balanced with the risk of recurrent disease from the known ipsilateral breast cancer, psychological and social issues of bilateral mastectomy, and the risks of contralateral mastectomy. The use of a prophylactic mastectomy contralateral to a breast treated with breast-conserving therapy is very strongly discouraged."

As part of a genetic/familial high-risk assessment for breast and ovarian cancer (v.3.2019), 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.21. In addition, the NCCN guidelines recommend that risk-reducing mastectomy be considered based on family history in women with certain genetic variants including CHEK2, STK11, and CDH1.

**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 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

**References**


**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**
- 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**
- 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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
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<tr>
<th>Type</th>
<th>Code</th>
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<td>Mastectomy, simple, complete</td>
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<td>19304</td>
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Policy History

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

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<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>07/31/2015</td>
<td>BC BSA Medical Policy adoption</td>
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<td>04/01/2016</td>
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<td>09/01/2017</td>
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<td>Policy statement clarification</td>
<td>Administrative Review</td>
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<td>Policy title change from Prophylactic Mastectomy</td>
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<tr>
<td>10/01/2019</td>
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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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 government 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 (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. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

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.