Medical Policy

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Title: Risk-Reducing Mastectomy

Professional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With high risk of breast cancer or extensive mammographic abnormalities precluding excision or biopsy	Interventions of interest are: • Risk-reducing mastectomy	Comparators of interest are: • Active surveillance • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Functional outcomes • Treatment-related morbidity
Individuals: • With unilateral breast cancer but are not otherwise at high risk	Interventions of interest are: • Contralateral risk-reducing mastectomy	Comparators of interest are: • Active surveillance • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Functional outcomes • Treatment-related morbidity

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.

OBJECTIVE

The objective of this policy is to evaluate whether risk-reducing mastectomy and/or contralateral risk-reducing mastectomy improves the net health outcome in individuals at risk for breast cancer.

BACKGROUND

Risk-reducing mastectomy may be considered in women thought to be at high risk of developing breast cancer, either due to a family history, presence of genetic variants such as BRCA1 or BRCA2, having received radiation therapy to the chest, or the presence of lesions associated with an increased cancer risk such as lobular carcinoma in situ. Lobular carcinoma in situ is both a risk factor for all types of cancer, including bilateral cancer, and in some cases a precursor for invasive lobular cancer. For those who develop invasive cancer, up to 35% may have bilateral cancer. 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 an invasive cancer (ie, contralateral risk-reducing mastectomy). The use of contralateral risk-reducing mastectomy has risen in recent years in the United States. An analysis of data from the National Cancer Data Base found that the rate of CPM in women diagnosed with unilateral stage I-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 risk, 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 5 risk factors: age at evaluation, age at menarche, age at first live birth, number of breast biopsies, and number of first-degree relatives with breast cancer. In addition to the patient's risk assessment, the choice of 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 versus other options.

* Characteristics of the Gail and Claus models
http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page1#Section/all

REGULATORY STATUS

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

POLICY

A. Unilateral or bilateral risk-reducing mastectomy may be considered **medically necessary** in patients at high risk of breast cancer with one of the following:

1. A known BRCA1 or BRCA2 variant**, OR**

2. Received radiotherapy to the chest between the ages of 10 and 30 years, **OR**

3. Presence of lobular carcinoma in situ, **OR**

4. Lifetime risk of developing breast cancer of 20% or greater as identified by models that are largely defined by family history**, OR**

5. Another gene variant associated with increased risk (eg, *TP53* (Li-Fraumeni syndrome), PTEN (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), *CDH1*, and *STK11*).

B. Risk-reducing mastectomy is considered **experimental / investigational** in individuals who do not meet high risk criteria.

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.

Policy Guidelines

1. It is strongly recommended that all candidates for risk-reducing mastectomy undergo counseling regarding cancer risks from a health professional skilled in assessing cancer risk other than the operating surgeon and discussion of the various treatment options, including increased surveillance or chemoprevention with tamoxifen or raloxifene.
2. 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.
3. 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 ≥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 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.

4. 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:
   a) History of breast cancer, ductal carcinoma in situ, breast augmentation, or mastectomy
   b) Age
   c) Race/ethnicity
   d) Number of first-degree relatives (mother, sister, or daughter) diagnosed with breast cancer
   e) Prior breast biopsies (positive or negative)
   f) BI-RADS breast density (radiologic assessment of breast tissue density by radiologists who interpret mammograms).

RATIONALE

The most recent literature search was performed for the period through May 7, 2018. Following is a summary of the key literature.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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. 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 Test Purpose

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

The question addressed in this evidence review is: Does risk-reducing mastectomy improve the net health outcome in women at high risk of breast cancer or extensive mammographic abnormalities precluding excision or biopsy?

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

Patients
The relevant population of interest is 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
- a known BRCA1 or BRCA2 variant
- another gene variant associated with high risk, eg, 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.

Comparators
The following practices are currently being used to make decisions about patients at high risk of breast cancer or who have extensive mammographic abnormalities precluding excision or biopsy: active surveillance and standard of care. Standard of care may involve chemoprevention.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, breast cancer incidence, and potential adverse events from the procedure.

Timing
To detect adverse events from the procedure, follow-up is postprocedure and may extend to a year. To measure breast cancer incidence and mortality, follow-up may extend 10 to 20 years.

Setting
Risk-reducing mastectomy is given in a tertiary care center.

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.[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 8 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 bilateral risk-reducing mastectomy on women with BRCA1 or BRCA2 variants.[4] 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], 0.4 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. to 100%.[5] These reviewers did not conduct pooled analyses of studies on the impact of a risk-reducing mastectomy on mortality.

Section Summary: Risk-Reducing Mastectomy
Evidence from systematic reviews has found that the incidence of breast cancer is reduced 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. Fewer studies have examined the impact of a risk-reducing mastectomy on overall or breast cancer-specific survival.

Contralateral Prophylactic Mastectomy

Clinical Context and Test Purpose
The purpose of contralateral risk-reducing mastectomy in patients who have unilateral breast cancer but are not otherwise at high risk is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of contralateral risk-reducing mastectomy improve the net health outcome in women with unilateral breast cancer but are not otherwise at high risk?

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

Patients
The relevant population of interest is women with unilateral breast cancer but are not otherwise at high risk.

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

Comparators
The following practices are currently being used to make decisions about patients with unilateral breast cancer but who are not otherwise at high risk: active surveillance and standard of care.

Outcomes
The general outcomes of interest are breast cancer incidence, OS, and disease-specific survival. Surgical complication rates are also of interest.

Timing
To detect adverse events from the procedure, follow-up is postprocedure and may extend to a year. To measure disease-related mortality, follow-up may extend 10 to 20 years.

Setting
Risk-reducing mastectomy is given in a tertiary care center.

Incidence of a Second Primary Breast Cancer
The potential for 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. 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%).[6] 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 assessing 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 a second primary breast cancer in women with and without BRCA1 or BRCA2 variants.[7] 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 a second primary breast cancer at 5 years after 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 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 was published by Fayanju et al (2014).[8] 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 085). 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 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 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 (eg, contralateral risk-reducing mastectomy recipients may be otherwise healthier and have better access to health care).

Studies in the Fayanju systematic review were published between 1997 and 2005. More recent large observational analyses are described below, several of which analyzed data from the SEER database.

Wong et al (2017) evaluated 496,488 women diagnosed with unilateral invasive breast disease.[9] 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<0.001). Patients were followed for a median of 8.25 years. In an analysis adjusting for age and other factors including stage of 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 cancerspecific 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 that 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.[10] 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. 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 077. (95% CI, 0.73 to 0.82). Presumably, 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 (25,924 women with unilateral mastectomy, 26,299 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-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 patients were not due to prevention of CBC but to selection bias (eg, 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.[1] The database collects information from 1450 Commission of Cancer–accredited cancer programs. The analysis included 219,983 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 5 years with contralateral risk-reducing mastectomy was 2. 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.[11] A total of 4338 (29.7%) of 14,627 women in this subgroup had a contralateral risk-reducing mastectomy. Median follow-up was 6. 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 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.[12] 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 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 lowapproximately 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.[13] 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.[14] The difference between groups was not statistically significant ($p=0.11$), but this study might have been underpowered. Eck 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 the 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. Relevant outcomes are overall survival, 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. Relevant outcomes are overall survival, 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.

CLINICAL INPUT RECEIVED 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, focused clinical input was received from 6 academic medical centers and 1 specialty society while this policy was under review in 2016. The focused clinical input addressed the issue 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. Clinical 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 developed a position statement on risk-reducing mastectomy in 1993 and updated it in 2007.[15] 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 updated its fact sheet in 2013 on risk-reducing surgery for breast cancer.[16] The fact sheet stated women with the following characteristics may consider bilateral prophylactic 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 2016 consensus statement from the American Society of Breast Surgeons made the following recommendations on contralateral risk-reducing mastectomy[17]:

- CPM (contralateral prophylactic mastectomy) should be considered for the following individuals at significant risk of contralateral breast cancer:
  - Documented *BRCA1* or *BRCA2* carrier
  - Strong family history in the absence of genetic testing
  - History of chest radiation before age 30
- CPM can be considered for the following individuals at lower risk of contralateral breast cancer:
  - Carrier of *CHEK*2, *PALB3*, *TP53*, or *CDHI*
  - Strong family history in *BRCA*-negative patients without 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 in the following situations:
  - "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 *BRCA*-positive family members
  - "Males with breast cancer, including *BRCA* carriers."

National Comprehensive Cancer Network

NCCN has made recommendations on several cancers relevant to this evidence review. On breast cancer risk-reduction (v.2.2018), 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 situs] 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."[18]

For invasive breast cancer (v.1.2018) NCCN has discouraged contralateral risk-reducing mastectomy, except for certain high-risk situations (noted in the risk-reduction guideline previously discussed).[19] 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 genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2018), 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.[20] In addition, 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 risk-reducing mastectomy have been identified.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov in June 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

CPT/HCPCS

19303	Mastectomy, simple, complete
19304	Mastectomy, subcutaneous

ICD-10 Diagnoses

C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast

C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
D05.01	Lobular carcinoma in situ of right breast
D05.02	Lobular carcinoma in situ of left breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.92	Unspecified type of carcinoma in situ of left breast
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z85.3	Personal history of malignant neoplasm of breast
Z40.01	Encounter for prophylactic removal of breast

REVISIONS

10-28-2011	Policy added to the bcbsks.com web site.
07-13-2012	Description section updated.
	In the Policy section: ▪ In Item #2, replaced "p" with "TP" to read "Presence of a TP53 or PTEN mutation" (Note—this was a clarification. No policy intent change.)
	Rationale section updated.
	Reference section updated.
11-29-2013	Updated Description section.
	In Policy section:

	▪ In Item A, removed "or moderately increased risk" to read "unilateral or bilateral prophylactic mastectomy may be considered medically necessary in patients at high risk of breast cancer with one of the following:" ▪ Removed Item A, #2 ▪ Removed Item A, #7-#18 ▪ Added new #6 to Item A, "Li-Fraumeni syndrome or Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome or a first-degree relative with one of these syndromes." ▪ Added Item B, "Prophylactic mastectomy is considered experimental / investigational in women who do not meet high risk criteria."
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis codes. *(Effective October 1, 2014)*
	Updated Reference section.
06-23-2015	Updated Description section.
	In Policy section: ▪ In Item A 1, removed "Presence of a" and added "or" to read "A known BRCA1 or BRCA2 mutation, OR" ▪ In Item A 2, removed "radiation therapy" and added "radiotherapy" and "or" to read "Received radiotherapy to the chest between the ages of 10 and 30 years, OR" ▪ In Item A 3, added "or" to read "Presence of lobular carcinoma in situ, OR" ▪ In Item A 4, added "or" to read "Extensive mammographic abnormalities (i.e., calcifications), OR ▪ In Item A 5, removed "the Gail or Claus model (Characteristics of the Gail and Claus models http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page1#Section_66)," and added "developing", "models that are largely defined by family history", "or" to read "Lifetime risk of developing breast cancer of 20% or greater as identified by models that are largely defined by family history, OR" ▪ In Item A 6, added "or" to read "Li-Fraumeni syndrome or Cowden syndrome or Banayan-Riley-Ruvalcaba syndrome or a first-degree relative with one of these syndromes, OR" ▪ Added Item A 7, "Another gene mutation associated with increased risk (e.g., PTEN, TP53, CDH1, and STK11)." ▪ In Policy Guidelines, removed "Cancer risk assessment should include a complete family history and use of the Gail or Claus model to estimate the risk of cancer." and "should be discussed", and added "other than the operating surgeon and discussion of the", to read "It is strongly recommended that all candidates for prophylactic mastectomy undergo counseling regarding cancer risks from a health professional skilled in assess cancer risk other than the operating surgeon and discussion of the various treatment options, including increased surveillance or chemoprevention with tamoxifen or raloxifene."
	Updated Rationale section.
	Updated References section.
10-01-2015	Policy published 05-25-2016. Retro-effective to 10-01-2015 with ICD-10 coding implementation.
	In Coding section: ▪ Added ICD-10 code: Z15.01.
05-25-2016	Updated Description section.
	Updated Rationale section.
	Updated References section.
06-08-2016	In Revision section: ▪ Removed "Updated Description, Updated Rationale, Updated References" sections from 10-01-2015 revision and created a 05-25-2016 revision.

11-22-2016	In Policy section: ▪ In Item B, removed "women" and added "individuals" to read, "Prophylactic mastectomy is considered experimental / investigational in women who do not meet high risk criteria."
10-28-2017	Updated Description section.
	In Policy section: ▪ In Item A 1, removed "mutation" and added "variant" to read, "A known BRCA1 or BRCA2 variant," ▪ Removed Item A 4, "Extensive mammographic abnormalities (ie, calcifications), OR". ▪ Removed Item A 6, "Li-Fraumeni syndrome or Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome or a first-degree relative with one of these syndromes, OR". ▪ In new Item A 5, removed "mutation" and added "variant", "(Li-Fraumeni syndrome)," and "(Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome)" to read, "Another gene variant, associated with increased risk (eg, *TI53* (Li-Fraumeni syndrome), PTEN (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), *CDH1*, and *STK11*)."
	Updated Rationale section.
	Updated References section.
09-12-2018	Revised title from "Prophylactic Mastectomy."
	Updated Description section.
	In Policy section: ▪ In Item A, removed "prophylactic" and added "risk-reducing" to read, "Unilateral or bilateral risk-reducing mastectomy may be considered medically necessary in patients at high risk of breast cancer with one of the following:" ▪ In Item B, removed "prophylactic" and added "risk-reducing" to read, "Risk-reducing mastectomy is considered experimental / investigational in individuals who do not meet high risk criteria." ▪ In Policy Guidelines, added new Item 4.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.

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