Prophylactic Mastectomy

I. Description

Prophylactic mastectomy (PM) is defined as the removal of the breast in the absence of malignant disease to reduce the risk of breast cancer occurrence.

The evidence for PM in women who have high risk of breast cancer or extensive mammographic abnormalities precluding incision or biopsy includes a TEC Assessment and systematic review of observational studies. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, and treatment-related morbidity. The studies found that PM reduces breast cancer incidence and increases survival in select patients. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcomes.

The evidence for contralateral prophylactic mastectomy (CPM) in women with breast unilateral cancer but are not otherwise at high risk includes observational studies. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, and treatment-related morbidity. Available studies do not clearly demonstrate a survival benefit in women without high-risk criteria. Moreover, there are potential risks (eg, surgical risks) associated with CPM. National guidelines, including those from the National Comprehensive Care Network, do not recommend that CPM be considered other than for certain high-risk women. The evidence is insufficient to determine the effects of the technology on health outcomes.

It is recommended that all candidates for prophylactic mastectomy consider undergoing a risk assessment from a health professional skilled in assessing cancer risk other than the operating surgeon. Cancer risk should be assessed by performing a complete family history, use of the Gail or Claus model to estimate the risk of cancer, and discussion of the various treatment options, including increased surveillance or chemoprevention with tamoxifen or raloxifene.

II. Criteria/Guidelines

A. Prophylactic mastectomy is covered (subject to Limitations and Administrative Guidelines) in patients at high risk of breast cancer, defined as having one or more of the following:
   1. Lobular carcinoma in situ
   2. A known BRCA1 or BRCA2 mutation
   3. Another gene mutation associated with high risk eg, TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), CDH1 and STK11.
4. High risk (lifetime risk about 20% or greater) of developing breast cancer as identified by models that are largely defined by family history.

5. Received radiation therapy to the chest between the ages of 10 and 30 years.

B. Prophylactic mastectomy is covered (subject to Limitations and Administrative Guidelines) in patients with such extensive mammographic abnormalities (i.e., calcifications) that adequate biopsy or excision is impossible.

III. Limitations
Prophylactic mastectomy is not covered for all other indications, including but not limited to contralateral prophylactic mastectomy in women with breast cancer who do not meet high risk criteria as it is not known to be effective in improving health outcomes.

IV. Administrative Guidelines
A. Precertification is not required. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria

B. Applicable Codes:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>19303</td>
<td>Mastectomy, simple, complete</td>
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<tr>
<td>19304</td>
<td>Mastectomy, subcutaneous</td>
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V. Background
Prophylactic 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 mutations 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 LCIS. LCIS 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 prophylactic mastectomy may be performed to eliminate the risk of cancer arising elsewhere; chemoprevention and close surveillance are alternative risk reduction strategies. Prophylactic 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.

The appropriateness of a prophylactic 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. Moreover, the choice of PM is based on patient tolerance for risk, consideration of changes to appearance and need for additional cosmetic surgery, and the risk reduction offered by PM versus other options.
VI. Rationale

The policy was initially based on a 1999 TEC Assessment that concluded that prophylactic mastectomy (PM) met the TEC criteria for patients with a family history of breast cancer. The Assessment largely focused on a 1999 retrospective cohort analysis which found that approximately 13 moderate-risk women would have to have PM 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 PM to prevent 1 occurrence of breast cancer.

As of 2014, the National Comprehensive Cancer Network guideline recommends that PM should only be considered in high-risk women, defined as a BRCA1 or BRCA2 mutation or another gene mutation associated with increased risk (eg, PTEN, TP53, CDH1, STK11), a compelling family history and possibly in women with lobular carcinoma in situ (LCIS) or prior thoracic radiation therapy before 30 years of age. Additional genetic mutations that have been associated with a high rate of cancer include TP53 (Li-Fraumeni syndrome) and PTEN (Cowden and Bannayan-Riley-Ruvalcaba syndromes. In patients who received prior radiation therapy to the chest between the ages of 10 and 30 years of age, the increased risk of breast cancer can reach almost 30% by age 55 years. Patients with LCIS, which is usually identified incidental to breast biopsy, are also at increased risk of cancer. In 2011, Oppong and King reported that, compared with the general population, women with LCIS face an 8- to 10-fold increased risk of cancer, equaling 26% after 20 years in 1 study.

A 2010 Cochrane review examined the impact of PM on mortality and other health outcomes. The authors did not identify any randomized controlled trials (RCTs). Thirty-nine observational studies with some methodologic-limitations were identified in the literature search. The studies presented data on 7,384 women with a wide range of risk factors for breast cancer who underwent PM. Studies on the incidence of breast cancer and/or disease-specific mortality reported reductions after PM, particularly for those with BRCA 1/2 mutations. The authors concluded that, while the available observational data suggest that bilateral PM reduces the rate of breast cancer mortality, more rigorous studies (ideally RCTs) are needed, and that bilateral PM should only be considered among patients at very high risk of disease.

Section Summary: Prophylactic Mastectomy

Evidence from systematic reviews found that reduction in breast cancer incidence is reduced and breast cancer survival is increased in women at high risk of breast cancer, especially those with BRCA1 or BRCA2 and selected other mutations and those with a compelling family history.

Contralateral Prophylactic Mastectomy

Incidence of Second Primary Breast Cancer

The potential for CPM 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% confidence interval [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 may be attributed at least in part to the increased availability of adjuvant hormone therapies.
Prophylactic Mastectomy

Survival
As is the case for bilateral PM, no RCTs evaluating the effect of CPM on health outcomes have been published. There are a number of observational studies, including some with large sample sizes, and a systematic review of 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.

Several observational analyses with large numbers of patients have been published. The study with the largest sample size was a 2014 systematic review and meta-analysis by Fayanju et al. The authors searched for published studies that compared the incidence of contralateral breast cancer in women with unilateral disease who did and did not undergo contralateral prophylactic mastectomy (CPM). The investigators did not differentiate between women who did and did not have risk factors such as certain genetic mutations or syndromes. Fourteen studies met eligibility criteria and were included in the meta-analysis; none were RCTs. In a meta-analysis of data from 6 studies, overall survival (OS) was significantly higher in the patients who underwent CPM (n=10,666) than those who had no CPM (n=145,490), relative risk (RR), 1.09 (95% confidence interval [CI], 1.06 to 1.11). Moreover, mortality from breast cancer was lower in the group that had CPM (RR, 0.69, 95% CI, 0.56 to 0.85, 4 studies). However, CPM was not associated with a reduction in the absolute risk of metachronous contralateral breast cancer (risk difference [RD], -18%, 95% CI, -42.0% to 5.9%, 8 studies). The authors commented that the improvement in survival after CPM in the general breast cancer population is likely not due to a decreased incidence of CBC, but rather is secondary to selection bias (eg, CPM recipients may be otherwise healthier and have better access to health care).

Other analyses have also concluded that the association between CPM and reduced mortality identified in data analyses can be attributed at least in part to selection of a healthier cohort of women for CPM. In particular, a 2014 analysis by Kruper et al of a large dataset from the SEER database looked at CBC and survival outcomes. The investigators conducted a case-control analysis including 28,015 CPM patients and 28,015 unilateral mastectomy patients, matched on age group, race/ethnicity, extent of surgery, tumor grade, tumor classification, node classification, estrogen receptor status, and propensity score. The investigators were not able to match for BRCA or other mutation status. When all matched patients were included, disease-specific survival (DSS) and OS were significantly lower in women who underwent unilateral mastectomy compared with CPM. For DSS, the hazard ratio (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, CPM 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 and 26,299 women with CPM). In the analysis excluding women with CBC, DSS and OS remained significantly lower in women who had unilateral mastectomy compared with CPM. 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 was not due to prevention of CBC, but instead to selection bias (eg, healthier women choosing CBC). A limitation of the analysis was the inability to control for risk factors including gene mutation status, family history, and a history of radiotherapy to the chest between ages 10 and 30 years.

In 2013, Yao et al evaluated overall survival after CPM by analyzing data from the National Cancer Data Base. The database collects data from 1450 Commission of Cancer-accredited cancer
programs. The analysis included 219,983 women who had mastectomy for unilateral breast cancer; 14,994 (7%) of these women underwent CPM at the time of their mastectomy surgery. The investigators did not report risk factors such as known genetic mutations. The overall 5-year survival rate was 80%. In an analysis adjusting for confounding factors, the risk of death was significantly lower in women who had CPM compared with women who did not have CPM. The adjusted hazard ratio (HR) was 0.88 (95% confidence interval [CI], 0.83 to 0.93). The absolute risk of death over 5 years with CPM was 2.0% lower than without CPM. In subgroup analyses, a survival benefit after CPM was found for individuals age 18 to 49 years and age 50 to 69 years, but not in patients 70 years or older. There was a survival benefit for women with stage I and II tumors, but not stage III tumors.

A subsequent study by Pesce et al, published in 2014, focused on the subgroup of patients who were young (<45 years-old) with stage I or II breast cancer. A total of 4338 of 10,289 women in this subgroup (29.7%) had CPM at the time of mastectomy surgery. Median follow-up was 6.1 years. In a multivariate analysis controlling for potentially confounding factors, OS did not differ significantly among patients who underwent unilateral mastectomy and those who additionally had CPM (HR, 0.93, 95% CI, 0.79 to 1.09). Moreover, among women younger than 45 years-old with estrogen-receptor negative cancer, there was no significant improvement in OS in those who underwent CPM versus unilateral mastectomy (HR, 1.13, 95% CI, 0.90 to 1.42).

There may be risks, as well as benefits, associated with CPM. In particular, several analyses have found higher rates of surgical complications in women undergoing CPM (bilateral mastectomy) versus unilateral mastectomy. Besides morbidity associated with these complications, surgical complications may delay receiving adjuvant therapy.

In 2015, Silva et al published a large multicenter study including 20,501 women with unilateral breast cancer from the American College of Surgeons National Surgery Quality Improvement Program (NSQIP) database. A total of 13,268 (64.7%) women underwent unilateral mastectomy and 7233 (35.3%) had bilateral mastectomy. The analysis did not report on high-risk factors such as BRCA mutation status or family history. All women had breast reconstruction; a higher proportion of women who had 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 versus unilateral mastectomy, regardless of reconstruction type. Among women with implant reconstructions, overall complication rates were 10.1% after bilateral mastectomy and 8.8% after unilateral mastectomy (adjusted odd ratio [OR], 1.20; 95% CI, 1.08 to 1.33). In women with autologous reconstructions, overall complication rates were 21.2% after bilateral mastectomy and 14.7% after 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 versus unilateral 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 for unilateral versus bilateral mastectomies.

Several single-center studies have also found significantly higher surgical complication rates after bilateral than unilateral mastectomy. For example, in a 2013 study by Miller et al, which included 600 women with unilateral breast cancer, CPM 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) than unilateral mastectomy. Moreover, in a 2014 study by Eck et al, 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 may have been underpowered. Moreover, the Eck study 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 had mixed findings on the survival benefit of CPM in women with unilateral breast cancer who do not otherwise meet high-risk criteria. Researchers have suggested that improvement in survival after CPM in the general breast cancer population found in some studies is due at least in part to selection bias. Moreover, there are risks (eg, surgical risks) of CPM.

Ongoing Clinical Trials

A search of ClinicalTrials.gov in January 2016 did not identify any ongoing RCTs or large observational studies.

Summary of Evidence

The evidence for PM in women who have high risk of breast cancer or extensive mammographic abnormalities precluding incision or biopsy includes a TEC Assessment and systematic review of observational studies. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, and treatment-related morbidity. The studies found that PM reduces breast cancer incidence and increases survival in select patients. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcomes. The evidence use of for contralateral prophylactic mastectomy (CPM) in women who have unilateral cancer but are not otherwise at high risk includes observational studies. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, and treatment-related morbidity. Available studies do not clearly demonstrate a survival benefit in women without high-risk criteria. Moreover, there are potential risks (eg, surgical risks) associated with CPM. National guidelines, including those from the National Comprehensive Care Network, do not recommend that CPM be considered other than for certain high-risk women. The evidence is insufficient to determine the effects of the technology on health outcomes.
Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN):
- Breast Cancer Risk Reduction, V.2.2015” risk reduction mastectomy should generally be considered only in women with genetic mutation conferring a high risk history for breast cancer (BRAC1, BRCA2, ATM, CDH1, CHEK2, PALB2, PTEN, STK11, and TP53, compelling family history, or possibly with LCIS or prior thoracic radiation therapy at <30 y of age.” The value of risk-reduction mastectomy in women with deleterious mutations in other genes associated with a 2-fold or greater risk for breast cancer (based on large epidemiologic studies) in the absence of a compelling family history of breast cancer is unknown.
- Breast cancer (v.2.2015), except for certain high-risk situations, noted in the risk reduction guideline previously discussed, CPM is discouraged. The guideline states: the small benefits from CPM in women with unilateral breast cancer must be balanced with the risk of recurrent disease from the ipsilateral breast cancer, psychosocial issues, 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.”

The Society of Surgical Oncology (SSO)
The SSO developed a position statement on prophylactic mastectomy in 1993. The position statement was updated in 2007 and indicates bilateral prophylactic mastectomy is potentially indicated in patients with:
- known BRCA 1 or 2 mutations or other genes that strongly predispose susceptibility to breast cancer,
- a history of multiple first-degree relatives with breast cancer history or multiple successive generations of breast and/or ovarian cancer, or
- biopsy-confirmed, high-risk histology such as atypical ductal or lobular hyperplasia or lobular carcinoma in situ [LCIS].
The SSO also indicates contralateral prophylactic mastectomy may be potentially indicated in patients:
- with high risk (as defined above) of contralateral breast cancer,
- in whom surveillance would be difficult such as with dense breast tissue or diffuse indeterminate microcalcifications, or
- to improve symmetry.

National Cancer Institute
The National Cancer Institute issued a fact sheet in 2012 on surgery to reduce the risk of breast cancer. The fact sheet provided the following information: Prophylactic surgery to remove both breasts (called bilateral prophylactic mastectomy) can reduce the risk of breast cancer in women who have a strong family history of breast and/or ovarian cancer, who have a deleterious (disease-causing) mutation in the BRCA1 gene or the BRCA2 gene, or who have certain breast cancer-associated mutations in other genes, such as TP53 and PTEN.

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for PM have been identified.
VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes § 432E-1.4), generally accepted standards of medical practice, and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA consider the application of this Medical Policy to the case at issue.

VIII. References