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 literature on PM primarily consists of observational studies and retrospective reviews; however, evidence demonstrates that PM reduces breast cancer incidence and increases survival in high-risk patients. Based on the scientific data consisting of large numbers of patients treated with follow-up, PM for breast cancer risk reduction may be considered medically necessary in patients at high risk of breast cancer. The choice of PM is based on patient tolerance for risk, consideration of the extreme disfiguration and need for additional cosmetic surgery, and the risk reduction offered by PM versus other options.

The use of contralateral prophylactic mastectomy (CPM) in women with unilateral cancer in the other breast has risen in recent years. There are insufficient data on a survival benefit of CPM, particularly for women who do not meet high-risk criteria. Moreover, there are potential risks, eg, operative risks associated with CPM. National guidelines, including from the National Comprehensive Care Network, do not recommend that CPM be considered other than for certain high-risk women. Thus, CPM is considered investigational in cases in which the woman does not meet criteria for high risk.

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. A known BRCA1 or BRCA2 mutation
2. At high risk of BRCA1 or BRCA2 mutation due to a known presence of the mutation in relatives.
3. Another gene mutation associated with increased risk (e.g., PTEN, TP53, CDH1 and STK11)
4. Li-Fraumeni syndrome or Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome or a first-degree relative with one of these syndromes.
5. High risk (lifetime risk about 20% to 25% or greater) of developing breast cancer as identified by models that are largely defined by family history.
6. 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.

C. Prophylactic mastectomy is covered (subject to Limitations and Administrative Guidelines) in patients with lobular carcinoma in situ (LCIS).

III. Limitations/Exclusions

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>
</tr>
</thead>
<tbody>
<tr>
<td>19303</td>
<td>Mastectomy, simple, complete</td>
</tr>
<tr>
<td>19304</td>
<td>Mastectomy, subcutaneous</td>
</tr>
</tbody>
</table>

V. Background

Prophylactic mastectomies 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.
Prophylactic Mastectomy

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.

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.

Contralateral Prophylactic Mastectomy

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 Fayanjlu 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 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. For example, a 2013 study by Miller et al evaluated potential risks associated with CPM at a single institution.11 Among 600 women treated for unilateral breast cancer, 391 (65%) underwent unilateral mastectomy and 209 (35%) underwent CPM. CPM patients tended to be diagnosed at an earlier stage than unilateral mastectomy patients and were less likely to undergo adjuvant therapy. A total of 402 patients underwent immediate reconstruction surgery, 55% of the unilateral mastectomy group and 90% of the CPM group. Overall, CPM patients had significantly more operative complications (112 [41.6%]) than unilateral mastectomy patients (87 [28.6%]; \(p<0.001\)). Moreover, there were more major complications in the CPM group. Twenty-nine (13.9%) patients in the CPM group and 16 (4.1%) patients in the unilateral mastectomy group experienced major complications \((p=0.001)\). The most frequent major complications were fixed tissue expander or implant control (CPM patients) and
seroma requiring reoperation in unilateral mastectomy patients. In multivariate analysis controlling for type of reconstruction and other factors such as adjuvant therapy and age, CPM remained associated with a significantly higher risk of any complication (odds ratio [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).

In addition, in 2014, Eck et al reported on 352 patients undergoing mastectomy for unilateral breast cancer.12 Within this cohort, 205 patients (58%) had unilateral mastectomy and 147 (42%) had bilateral mastectomy. A total of 94 women (27%) had complications, 48 (23%) in the unilateral mastectomy group and 46 (31%) in the bilateral mastectomy group, p=0.11. Morbidity occurred only in the prophylactic breast in 19 women (13% of those undergoing CPM); 10 of these patients required reoperation. Women with complications had a longer time before receiving adjuvant therapy compared with those without complications (49 days vs 40 days, p<0.001).

Ongoing Clinical Trials
A search of ClinicalTrials.gov in December 2014 did not identify any ongoing RCTs or large observational studies.

Summary of Evidence
Prophylactic mastectomy is defined as the removal of the breast in the absence of malignant disease to reduce the risk of breast cancer occurrence. The literature on PM primarily consists of observational studies and retrospective reviews; however, evidence demonstrates that PM reduces breast cancer incidence and increases survival in high-risk patients. Based on the scientific data consisting of large numbers of patients treated with follow-up, PM for breast cancer risk reduction may be considered medically necessary in patients at high risk of breast cancer. The choice of PM is based on patient tolerance for risk, consideration of the extreme disfiguration and need for additional cosmetic surgery, and the risk reduction offered by PM versus other options.

The use of contralateral prophylactic mastectomy in women with unilateral cancer in the other breast has risen over the last decade or two. The increase does not appear to be limited to women at high risk of cancer, although this characteristic is not reported in every study. The factors behind this increase continue to be explored. Contralateral prophylactic mastectomy is not covered considered in cases where the woman does not meet criteria for high risk.

Supplemental Information
Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN):

- Breast Cancer Risk Reduction, 2014 (V.1): risk reduction mastectomy should generally be considered only in women with genetic mutation conferring a high risk history for breast cancer (BRCA 1/2, PTEN, TP53, CDH1, STK11), 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.
2014 (V.3) breast cancer guideline state that, except for certain high-risk situations, CPM is discouraged. NCCN notes that 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

The U.S. Preventive Services Task Force published recommendations for breast cancer screening, entitled BRCA-Related Cancer Risk Assessment, Genetic Counseling and Genetic Testing, in December 2013. They have also issued a recommendation stating that women at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications such as tamoxifen or raloxifene. Prophylactic mastectomy was not addressed.
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.

VII. References