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. 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 lobular carcinoma in situ (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.

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/Exclusions 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. Li-Fraumeni syndrome or Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome or a first-degree relative with one of these syndromes.
   4. 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.
   5. Received radiation therapy to the chest between the ages of 10 and 30 years.

B. Prophylactic mastectomy is covered (subject to Limitations/Exclusions 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/Exclusions and Administrative Guidelines) in patients with 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>
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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. Rationale

This policy is based on a 1995 Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Committee (TEC) Assessment that concluded that prophylactic mastectomy met the TEC criteria for patients with a family history of breast cancer.

The TEC Assessment focused on one 1999 study, a retrospective cohort analysis of 639 women with a family history of breast cancer who underwent bilateral prophylactic mastectomy between 1960 and 1993 at the Mayo Clinic. The patients were subdivided into 2 groups: high-risk patients had a
family history suggestive of hereditary breast cancer (n=214), while the remaining 425 patients were arbitrarily considered to have a moderately increased risk. However, it should be emphasized that all women had some sort of family history of breast cancer. For each group, the reduction in the incidence of mortality due to breast cancer was estimated by comparison to a control group (sisters of high-risk patients) or predicted outcomes (using the Gail model for moderate-risk patients). For patients at moderate risk of breast cancer, 37.4 cancers were predicted by the Gail model, and 4 were observed for an incidence reduction of 89.5%. Approximately 13 moderate-risk women would have to have prophylactic mastectomy to prevent one cancer. For those at high risk of breast cancer, reduction in breast cancer incidence ranged from 90%–94%. Four to eight high risk women would need to undergo prophylactic mastectomy to prevent one occurrence of breast cancer.

While all patients in the Hartmann study had a family history of breast cancer, it should not be concluded that all patients with a family history of breast cancer are candidates for a prophylactic mastectomy. There is a broad spectrum of family history, ranging from those at high risk due to a family history consistent with hereditary breast cancer to those at more moderate risk, ie, with a single affected relative. The decision is a complicated patient-driven risk-benefit analysis of the individual cancer risk. While the cancer risk is greatest for those considered at high risk, whether or not the cancer risk associated with moderate-risk patients warrants a prophylactic mastectomy is a difficult question. While high risk is more objectively defined either by a family history alone or the presence of a BRCA1 or BRCA2 mutation, moderate risk may be conferred by a wide range of family histories in association with different breast pathologies.

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, 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. In a commentary on this review, Visvanathan noted that up to 35% of these women who develop breast cancer have bilateral disease, which is why some undergo bilateral prophylactic mastectomy. In a second commentary, Visscher and Hartmann stated that the distinction between LCIS and atypical lobular hyperplasia is often problematic and based on the degree of lobular involvement. More generally, considerable uncertainty exists about the nature and optimal treatment for LCIS, despite some useful findings from genetic profiling.

Impact of PM on health outcomes

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 BPM, particularly for those with BRCA 1/2 mutations. For contralateral prophylactic mastectomy (CPM), studies consistently reported reductions in incidence of contralateral breast cancer but were inconsistent about improvements in disease-specific survival. 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. Moreover, they concluded that there is insufficient evidence that CPM increases survival.

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 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. Data were not available to do subgroup analyses according to the presence or absence of genetic mutations or family history risk factors.

In a 2011 study of 2,965 mastectomy patients for unilateral cancer at Memorial Sloan-Kettering Cancer Center, 407 (13%) underwent either immediate (90%) or delayed (within 1 year) CPM. Of the patients undergoing CPM, 69% had a family history of breast cancer, 34% had completed clinical genetic counseling, and 9% (37 patients) had BRCA 1/2 mutations. The mean age was 44.8 years (range, 20-80). Sixty-three percent of the index (i.e., ipsilateral) cancers were invasive ductal cancer, 22% were pure ductal carcinoma in situ (DCIS), 9% were invasive lobular cancers, and 7% were infiltrating mammary (mixed) cancers. Based on histologic findings from the CPM specimens, 6% of the women had contralateral cancer and 28% had a “high-risk lesion”, defined as atypical ductal or lobular hyperplasia or LCIS. The authors report a 4- to 5-fold increased risk of developing breast cancer for women with atypical ductal hyperplasia (based on studies from the 1990s) and 8- to 9-fold for women with LCIS (based on studies from the 1970s and early 2000s). On multivariate analysis, patient age (>50) (OR=3.09; 95% CI: 1.682 to 5.692; p=0.0003) and progesterone receptor positivity (OR=3.37; 95% CI: 1.651 to 6.871; p=0.0008) were significantly associated with either malignancy or high-risk lesion compared to having only benign findings. The odds ratio for use of hormone replacement therapy for more than one year was 2.45 (95% CI: 1.021 to 5.865; p=0.0447). The authors did not adjust for multiple comparisons because of the “retrospective and exploratory” nature of the analysis.

Chung and colleagues compared the characteristics of 177 women undergoing CPM with 178 age- and stage-matched controls at a single institution. The median age at diagnosis was 48.5 years (range, 24-82). Of the 355 patients, 19.1% had DCIS and the remainder had invasive disease. There
was no difference between those who underwent CPM and those who did not in terms of histology, grade, hormone-receptor status, or presence of multifocality. Women who had CPM were twice as likely to have undergone preoperative magnetic resonance imaging (MRI) (p<0.001). Patients in the CPM group were statistically significantly more likely to have a history of previous breast biopsy, family history of breast cancer, or BRCA gene mutation. Histopathology of the contralateral breast found that 6.6% of the women undergoing CPM had occult cancer; 7 of 11 patients had DCIS. With a median follow-up of 61 months (range, 2-171 months), 1.7% of the women who did not undergo CPM had developed contralateral breast cancer.

Ongoing Clinical Trials

A search of online site ClinicalTrials.gov in February 2014 found one registry study of prophylactic mastectomy for breast cancer risk reduction. This registry will examine patient quality of life, cancer occurrence, adverse events, and survival annually for 10 years (NCT00555503). The study aims to enroll 500 women.

Summary

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.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN):

- 2013 (V.1) breast cancer risk reduction guideline states that risk reduction mastectomy (i.e., PM) should “generally be considered only in women with BRCA1/2, or other strongly predisposing gene mutation, compelling family history, or possibly with LCIS or prior thoracic radiation therapy at <30 y of age.” (3)

- 2014 (V.1) breast cancer guideline state that, except for certain high-risk situations, CPM is discouraged. (12) 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 risks of CPM.

The Society of Surgical Oncology (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.

VI. 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