BlueCross BlueShield of Louisiana

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Prophylactic Mastectomy

Policy # 00141
Original Effective Date: 09/27/2004
Current Effective Date: 10/16/2013

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider prophylactic mastectomy in patients at high risk or moderately increased risk of breast cancer to be **eligible for coverage**.

Based on review of available data, the Company may consider prophylactic mastectomy in patients with lobular carcinoma in situ to be **eligible for coverage**.

High Risk Patient Selection Criteria:
Coverage eligibility will be considered for prophylactic mastectomy in patients at high risk of breast cancer when ANY of the following criteria are met:

- Two or more first-degree relatives with breast cancer or ovarian cancer; or
- One first-degree relative and two or more second-degree or third-degree relatives with breast cancer; or
- One first-degree relative with breast cancer before the age of 45 years and one other relative with breast cancer; or
- One first-degree relative with breast cancer and one or more relatives with ovarian cancer; or
- Two second-degree or third-degree relatives with breast cancer and one or more with ovarian cancer; or
- One second-degree or third-degree relative with breast cancer and two or more with ovarian cancer; or
- Three or more second-degree or third-degree relatives with breast cancer; or
- One first-degree relative with bilateral breast cancer; or
- A known BRCA1 or BRCA2 mutation; or
- Presence of a TP53 or PTEN mutation; or
- Received radiation therapy to the chest between the ages of 10 and 30 years.

Note: The above definition of high risk is largely adapted from Hartmann (see Hartmann et al, 1999, in Rationale section).

Moderate Risk Patient Selection Criteria:
Coverage eligibility will be considered for prophylactic mastectomy in patients at moderately increased risk of breast cancer when ANY of the following criteria are met:

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- Those who do not meet the definition of high risk, but nonetheless are considered at moderately increased risk based on family history with or without breast lesions associated with an increased risk, including, but not limited to, atypical hyperplasia or breast cancer diagnosed in the opposite breast. For this policy, increased risk is defined as a lifetime risk of breast cancer of 20% or greater as identified by models that are largely defined by family history such as the Gail or Claus model; or
- Patients with such extensive mammographic abnormalities (i.e., calcifications) that adequate biopsy is impossible.

It is recommended that all candidates for prophylactic mastectomy consider undergoing counseling regarding cancer risks 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.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers prophylactic mastectomy for all other indications, including but not limited to contralateral prophylactic mastectomy in women with breast cancer who do not meet risk criteria to be **investigational.***

Background/Overview

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 PM 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 PM 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.

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Rationale/Source

The most recent literature search was performed for the period July 2011 through February 5, 2013. Following is a summary of key findings.

This policy was initially based on a 1999 TEC Assessment that concluded that PM met the TEC criteria for patients with a family history of breast cancer. However, patients with a family history represent a broad spectrum, ranging from those at high risk due to a family history consistent with hereditary breast cancer to those at more moderate risk, i.e., with a single affected relative.

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 PM between 1960 and 1993 at Mayo Clinic. A total of 90% of the mastectomies were subcutaneous. 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 PM to prevent 1 cancer. For those at high risk of breast cancer, reduction in breast cancer incidence ranged from 90–94%. Four to 8 high-risk women would need to undergo PM to prevent 1 occurrence of breast cancer.

While all patients in the Hartmann et al. 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 PM. Essentially 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 PM 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.

The Hartmann et al. study evaluated by the TEC Assessment was a retrospective cohort study that arbitrarily assigned all women not at high risk to be at moderate risk. It is not known what kind of risk assessment was performed, if any, prior to the mastectomy procedure. In the study, of the 425 women in the moderate-risk category, 268 had at least 1 affected first-degree relative, 46 had 2 aunts, cousins, or both with breast cancer and fewer second-degree or third-degree relatives. This group includes a wide variety of patients, with the spectrum potentially ranging from a patient with a first-degree relative with bilateral premenopausal breast cancer to a patient whose elderly mother is diagnosed with breast cancer. The Gail model has been used as patient selection criteria to identify women at increased risk of breast cancer who would be candidates for chemoprevention with tamoxifen. The Breast Cancer Chemoprevention Trial accepted patients between the ages of 35 and 59 years with a 5-year predicted risk of breast cancer of

1.66%, according to the Gail model. Presumably, at the very least, the predicted cancer risk of candidates for PM should exceed that of candidates for chemoprevention.

Additional factors have been associated with a high rate of cancer including the pTP53 (Li-Fraumeni syndrome) and PTEN (Cowden and Bannayan-Riley-Ruvalcaba syndromes) genetic mutations. Patients who received prior radiation therapy to the chest between the ages of 10 and 30 years of age also have an increased risk of breast cancer which 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. Two reviewers report that compared to the general population, women with LCIS face an 8- to 10-fold increased risk of cancer, equaling 26% after 20 years in one 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 state that the distinction between LCIS and atypical lobular hyperplasia is often problematic and based on the degree of lobular involvement. More generally, there appears to be considerable uncertainty about the nature and optimal treatment for LCIS, despite some useful findings from genetic profiling.

An updated Cochrane review was published by Lostumbo and colleagues in 2010. The 39 included studies were observational studies with some methodologic limitations. There were no randomized trials. The studies presented data on 7,384 women with a wide range of risk factors for breast cancer who underwent PM. Bilateral prophylactic mastectomy (BPM) 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. Sixteen studies assessed psychosocial measures; most of these reported high levels of satisfaction with the decision to have PM but more variable satisfaction with cosmetic results. Worry over breast cancer was significantly reduced after BPM when compared to baseline worry levels. Case series reporting on adverse events from PM with or without reconstruction reported rates of unanticipated re-operations from 4% in those without reconstruction to 49% in patients with reconstruction. The authors' summary and conclusions are as follows: "Sixteen observational studies have been published since the last version of the review, without altering our conclusions. While published observational studies demonstrated that BPM was effective in reducing both the incidence of, and death from, breast cancer, more rigorous prospective studies (ideally randomized trials) are needed. BPM should be considered only among those at very high risk of disease. There is insufficient evidence that CPM improves survival and studies that control for multiple confounding variables are needed."

Many published studies identified in literature review updates reported on factors that influenced decisions about PM. Studies also discussed both patient satisfaction and quality of life after the procedure. Additionally, studies on comparative/cost effectiveness supporting PM versus surveillance have been identified.

A number of studies in recent years have pointed to the increasing use in the United States of CPM in women with a diagnosed breast cancer in the other breast. In a study based on the American College of Surgeons' National Cancer Data Base, use of CPM increased from 0.4% of women diagnosed with

unilateral breast cancer in 1998 to 4.7% in 2005, for a total of 23,218 CPMs of the 1,166,456 cases reviewed. Patient's average age was 61.2 years. Data on genetic mutations in these patients was not reported. But in a multivariable analysis, the authors found that the greatest comparative increases between 1998-1999 versus 2006-2007 was among white patients younger than 40-years old residing in areas of high socioeconomic status, who had private or managed care insurance plans, and were treated at high-volume medical centers in the Midwest. Women with in situ disease were more likely to have CPM.

In a 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. The percentage undergoing CPM rose from 6.7% (15 patients) in 1997 to 24.2% (119 patients) in 2005. 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 ($\geq$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. The proportion of women undergoing CPM to treat unilateral breast cancer increased from 19.4% in 1995-1999 to 56.6% during 2000-2004 and 64.7% during 2005-2008 (p<0.0001). 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.

Two other factors should be noted regarding CPM: First, the index (ipsilateral cancer) poses the greatest risk to the patient. Second, the use of endocrine therapy reduces the risk of contralateral breast cancer.

Ongoing Clinical Trials
A search of online site ClinicalTrials.gov in February 2013 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). There is also a trial on decision making regarding prophylactic mastectomy and oophorectomy in women seeking genetic counseling and testing for BRCA1/2 mutations, that is active but no longer recruiting patients (NCT00579007).

Summary
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 prophylactic mastectomy primarily consists of observational studies and retrospective reviews; however, evidence demonstrates that prophylactic mastectomy 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, prophylactic mastectomy 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 considered investigational in cases where the woman does not meet criteria for high risk.

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Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	19303, 19304
HCPCS	No code
ICD-9 Diagnosis	V16.3, V50.41
ICD-9 Procedure	85.33, 85.34, 85.35, 85.36, 85.41, 85.42

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08/31/2004	Medical Director review
09/21/2004	Medical Policy Committee review
09/27/2004	Managed Care Advisory Council approval
09/07/2005	Medical Director review
09/20/2005	Medical Policy Committee review Coverage eligibility unchanged
09/22/2005	Quality Care Advisory Council approval

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07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
10/04/2006	Medical Director review
10/18/2006	Medical Policy Committee approval. Policy statement unchanged. Addition of FDA and or other governmental regulatory approval. References added.
10/10/2007	Medical Director review
10/17/2007	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009	Medical Policy Committee approval
10/14/2009	Medical Policy Implementation Committee approval. Added moderately increased risk for breast cancer to be eligible for coverage with criteria. Added last two criteria bullets for high risk breast cancer.
10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval. The term “p53” was updated to the more current “TP53” terminology in the Patient Selection Criteria.
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. High risk criteria revised to track BCBSA. Investigational statement reworded to track BCBSA.

Next Scheduled Review Date: 10/2014

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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