Cigna Medical Coverage Policy

Effective Date ....................... 8/15/2014  
Next Review Date ..................... 8/15/2015  
Coverage Policy Number ............ 0029

Subject  Prophylactic Mastectomy

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Coverage Policy

Cigna covers prophylactic mastectomy as medically necessary for the treatment of individuals at high risk of developing breast cancer when any ONE of the following criteria is met:

Individuals with a personal history of cancer as noted below:

- individuals with a personal history of breast cancer when any ONE of the following criteria is met:
  - diagnosed at age 45 or younger  
  - diagnosed at age 50 or younger with at least one close blood relative* with breast cancer at any age  
  - diagnosed with two breast primaries (includes bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors) when the first breast cancer diagnosis occurred prior to age 50  
  - diagnosed at age 60 or younger with a triple negative breast cancer  
  - diagnosed at age 50 or younger with a limited family history (e.g., fewer than two first- or second degree female relatives or female relatives surviving beyond 45 years in the relevant maternal and/or paternal lineage)  
  - diagnosed at any age and there are at least two close blood relatives* with breast cancer diagnosed at any age
- diagnosed at any age and there is at least one close blood relative* with breast cancer at age 50 or younger
- diagnosed at any age and there are at least two close blood relatives* with pancreatic cancer or prostate cancer (Gleason score ≥7) at any age
- diagnosed at any age with one or more close blood relatives* with epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer
- close male blood relative* with breast cancer
- an individual of Ashkenazi Jewish descent
- development of invasive lobular or ductal carcinoma in the contralateral breast after electing surveillance for lobular carcinoma in situ of the ipsilateral breast
- lobular carcinoma in situ confirmed on biopsy
- lobular carcinoma in situ in the contralateral breast
- diffuse indeterminate microcalcifications or dense tissue in the contralateral breast that is difficult to evaluate mammographically and clinically
- a large and/or ptotic, dense, disproportionately-sized contralateral breast that is difficult to reasonably match the ipsilateral cancerous breast treated with mastectomy and reconstruction

- personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer
- personal history of pancreatic cancer or prostate cancer (Gleason score ≥7) at any age with two or more close blood relatives* with breast, ovarian, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
- personal history of pancreatic cancer at any age with Ashkenazi Jewish ancestry and one or more close blood relatives* with breast, ovarian, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
- personal history of male breast cancer

Individuals with no personal history of breast or epithelial ovarian cancer when any ONE of the following is met:

- known breast risk cancer antigen (BRCA1 or BRCA2), p53 or PTEN mutation confirmed by genetic testing
- close blood relative* with a known BRCA1, BRCA2, p53 or PTEN mutation
- first- or second-degree blood relative* meeting any of the above criteria for individuals with a personal history of cancer
- third-degree blood relative with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer with two or more close blood relatives* with breast and/or ovarian cancer (with at least one close blood relative with breast cancer prior to age 50)
- history of treatment with thoracic radiation
- atypical ductal or lobular hyperplasia, especially if combined with a family history of breast cancer
- dense, fibronodular breasts that are mammographically or clinically difficult to evaluate, several prior breast biopsies for clinical and/or mammographic abnormalities, and strong concern about breast cancer risk

*A close blood relative/close family member includes first-, second-, and third-degree relatives on the same side of the family.
A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.
A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.
A third-degree relative is defined as a blood relative with whom an individual shares approximately 12.5% of his/her genes, including the individual's great-grandparents and first-cousins.

General Background

Breast cancer accounts for one-third of all cancers in women. Known risk factors for breast cancer include age, early menarche, nulliparity, age at first live birth, radiation exposure, atypical hyperplasia, and family history.
Approximately 5–10% of breast tumors are hereditary; the remaining cases are caused by genetic changes that occur during a woman’s life and are commonly called sporadic. Women who test positive for breast risk cancer antigen (BRCA1/BRCA2) mutations, which are located on chromosome 17q21 and 13q12–q13, respectively, carry a 60–85% lifetime risk of breast cancer and a 15–65% cumulative lifetime risk of invasive epithelial ovarian cancer. Breast/ovarian cancer predisposition is passed on from generation to generation in an autosomal dominant pattern, through maternal or paternal lineage. When a parent carries an autosomal dominant genetic predisposition, each child has a 50% chance of inheriting the predisposition. However, not everyone with the predisposition will develop cancer. Both males and females can inherit and transmit an autosomal dominant cancer predisposition ([National Cancer Institute [NCI]], 20134). Male breast cancer is rare, accounting for less than 1% of all breast cancer cases. Nonetheless, inheritance of a breast cancer susceptibility gene, especially the BRCA2, is associated with these rare breast cancers as well ([NCI], 2014b). Males with a BRCA2 mutation have a 6% risk of developing breast cancer by the age of 70 (Agrawal, et al., 2006).

In addition, there are some histopathologic features that have been noted to occur more frequently in breast cancers that associated with BRCA1 or BRCA2 mutation. Several studies have demonstrated that BRCA1 breast cancer is more likely to be characterized as estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER2) negative, also referred to as triple negative breast cancer. Studies have reported BRCA1 mutations in 11% to 28% of patients with triple-negative breast cancer. It has also been noted that in patients with triple-negative disease, the BRCA mutation carriers were diagnosed at a younger age compared to non-carriers ([National Comprehensive Cancer Network® [NCCN®]], 2014a).

Breast cancer is also a component of Li-Fraumeni syndrome, in which germline mutations in the p53 gene on the short arm of chromosome 17 have been documented. The tumor suppressor gene p53 mutation is observed in 77% of Li-Fraumeni syndrome families. Inheritance of the syndrome is autosomal-dominant. The condition is characterized by multiple tumors in the same individuals and clustering of tumors within the same family. The Li-Fraumeni gene is thought to account for less than 1% of all breast cancers. Germline mutations in the protein tyrosine phosphatase with homology to tensin (PTEN) gene located on chromosome 10q23 are responsible for Cowden syndrome. This syndrome is also rare with an autosomal-dominant pattern of inheritance. Cowden syndrome is characterized by conditions that include an excess of breast cancer, gastrointestinal malignancies, and both benign and malignant thyroid disease. Lifetime estimates for breast cancer among women with Cowden syndrome range from 25%—50%. Like other forms of breast cancer, Cowden syndrome occurs at a young age and may be bilateral ([NCCN, 2014a]). Other breast and/or ovarian cancer susceptibility genes include STK11 and CDH1. Germline mutations in the STK11 gene are associated with Peutz-Jeghers syndrome, which is characterized by gastrointestinal polyps and an increased risk of gastrointestinal, breast, or ovarian cancer. A cumulative lifetime risk for breast cancer of 39%-52% has been reported for women who carry CDH1 mutations ([NCCN, 2014a]).

With the identification of high-risk individuals, prophylactic measures (e.g., surgery, tamoxifen chemoprevention, or increased surveillance) can be taken to decrease the risk of cancer occurrence or recurrence. Prophylactic mastectomy is the surgical removal of one or both breasts before cancer develops. Either the whole breast (i.e., total or simple mastectomy) or the underlying breast tissue excluding the nipple (i.e., subcutaneous mastectomy) is removed. The "gold standard" and most widely used form of prophylaxis is a total or simple mastectomy, since it removes more breast tissue. Reconstruction may occur immediately or be delayed. Because the surgery is not removing cancer, the lymph nodes are left intact. Some of the reasons for considering prophylactic mastectomy may include ([American Cancer Society [ACS]], 2014):

- mutated BRCA genes found by genetic testing
- previous cancer in one breast (especially in someone with a strong family history)
- strong family history (breast cancer in several close relatives)
- biopsy specimens showing lobular carcinoma in situ (LCIS)

Women ≥ 35 years of age without BRCA1/2, p53, or PTEN mutation, a strong family history of breast cancer, a history of thoracic radiation before age 30, or history of LCIS should have their risk for breast cancer estimated according to the Gail model ([NCCN, 2014b]). This computerized risk-assessment program assesses risks using such factors as age, age at menarche, age of first live birth, ethnicity, first-degree relatives with breast cancer, as well as number and histology of previous breast biopsies.
Literature Review
A Cochrane review by Lostumbo et al. (2010) concluded that BPM should only be considered by those at very high risk for breast cancer. It was found that while published observational studies (n=39; 7384 subjects) showed that BPM was effective in reducing both the incidence of and mortality from breast cancer more rigorous prospective studies are needed. For CPM, studies consistently reported reductions in contralateral incidence of breast cancer but were inconsistent about improvements in disease-specific survival.

A systematic review by Bermejo-Pérez and colleagues (2007) included systematic reviews (n=2), cohort studies (n=10), and case-control studies (n=6). The review assessed the effectiveness of preventive intervention strategies (i.e., prophylactic surgery, intensive cancer screening, and chemoprevention) implemented in women carrying mutations in BRCA1 or BRCA2 genes, in terms of reducing breast and gynecological cancer incidence and/or mortality. Selection bias was the primary methodological flaws identified in these studies. BPM compared to surveillance was found to reduce the incidence of breast cancer in women carrying BRCA gene mutations with no previous history of cancer. Results from a single study (n=148) with three-year follow-up indicated that CPM versus surveillance reduced the incidence of contralateral breast cancer in women with unilateral breast cancer carrying BRCA gene mutations (Bermejo-Pérez, et al., 2007).

A number of prospective and retrospective studies have evaluated the effectiveness of prophylactic mastectomy for breast cancer reduction in women with known BRCA1 and BRCA2 mutations and with known family histories of breast and/or ovarian cancer (Rebbeck, et al., 2004; Meijers-Heijboer, et al., 2001; McDonnell, et al., 2001; Peralta, et al., 2000; Hartman, et al., 1999). In general, the results of these studies indicate that prophylactic mastectomy results in risk reduction of breast cancer occurrence by at least 90% for women in moderate- and high-risk groups.

Professional Societies/Organizations
According to the National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™) for genetic/familial high-risk assessment of breast and ovarian cancer, it is generally accepted that carriers of mutation in BRCA1 or BRCA2 have an excessive risk for both breast and ovarian cancer that warrants consideration of more intensive preventive and screening strategies. In addition, characteristics of hereditary breast and/or ovarian cancer (HBOC) syndrome in individuals with a personal history of breast cancer include onset of the disease at an early age, Ashkenazi Jewish ancestry, any male breast cancer and a family history of breast and/or ovarian cancer. Individuals who have only a family history of breast and/or ovarian cancer may also be at risk. The guidelines for HBOC contain criteria for referral to risk assessment, counseling, and consideration of genetic testing and risk reduction. Genetic testing criteria include the following (NCCN, 2014a):

- individual from a family with a known BRCA1/BRC2A mutation
- personal history of breast cancer (including invasive and ductal carcinoma in situ breast) plus one or more of the following:
  - diagnosed at age ≤45 years
  - two breast primaries (including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors) when first breast cancer diagnosis occurred prior to age 50
  - diagnosed at age 60 or younger with a triple negative breast cancer
  - diagnosed at age ≤50 years with one or more close blood relative* with breast cancer at any age
  - diagnosed at age 50 or younger with a limited family history (e.g., fewer than two first- or second degree female relatives or female relatives surviving beyond 45 years in either lineage)
  - diagnosed at any age, with two or more close blood relatives* with breast cancer at any age
  - diagnosed at any age with two or more close blood relatives* with pancreatic cancer at any age
  - diagnosed at any age and there is at least one close blood relative* with breast cancer at age 50 or younger
  - diagnosed at any age and there are at least two close blood relatives* with prostate cancer (Gleason score ≥7) at any age
  - diagnosed at any age with one or more close blood relative with epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer
  - close male blood relative with breast cancer
for an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish), no additional family history may be required

- personal history of epithelial ovarian (includes fallopian tube and primary peritoneal) cancers
- personal history of male breast cancer
- personal history of pancreatic cancer or prostate cancer (Gleason score ≥7) at any age with two or more close blood relatives* with breast, and/or ovarian (includes fallopian tube and primary peritoneal cancers) and/or pancreatic cancer or prostate cancer (Gleason score ≥7) at any age (for pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional relative is needed)
- family history only with one of the following (Clinical judgment should be used to determine if the patient has a reasonable likelihood of a mutation, considering the unaffected patient’s current age and the age of female unaffected relative who link the patient with the affected relatives. Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing. Significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative with breast and/or ovarian (includes fallopian tube and primary peritoneal) cancer with two or more close blood relatives with breast cancer (at least one with breast cancer ≤50 years) and/or ovarian cancer

*A close blood relative/close family member includes first-, second-, and third-degree relatives on the same side of the family.

The NCCN states that risk-reducing mastectomy should generally be considered only in women with a genetic mutation that is associated with a high risk of breast cancer, compelling family history, or possibly with LCIS or previous thoracic radiation therapy younger than 30 years of age (NCCN, 2014a; 2014b).

The U.S. Preventive Services Task Force (USPSTF) issued guidelines for management of BRCA-related cancer in women. According to the USPSTF, interventions that may reduce risk for cancer or cancer-related death in women who are BRCA mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications (e.g., tamoxifen or raloxifene); and risk-reducing surgery (e.g., mastectomy or salpingo-oophorectomy). However, the strength of evidence varies across the types of interventions. In high-risk women and those who are BRCA mutation carriers, cohort studies of risk-reducing surgery (mastectomy and salpingo-oophorectomy) showed substantially reduced risk for breast or ovarian cancer, with a risk reduction of 85%-100% with mastectomy (Moyer, et al., 2014).

According to the American Society of Plastic Surgeons’ (ASPS) coverage criteria for prophylactic mastectomy, groups at a high risk for developing breast cancer include women with a family history of breast cancer in first- and second-degree relatives or those who carry the BRCA1 or BRCA2 gene. These women have a lifetime risk of breast cancer estimated from 60–90%. Patients who have had breast cancer at an early age (<40 years) have an increased lifetime risk of developing breast cancer in the contralateral breast. These patients may seek a prophylactic mastectomy, which carries a risk reduction of greater than 90% in high-risk women with or without the BRCA1 or BRCA2 gene. Other groups of women at high risk include those with atypical hyperplasia and fibrocystic breast disease and pathologic findings showing diffuse microcalcifications, lobular carcinoma in situ (LCIS) or invasive lobular cancer. Males who have had breast cancer, especially those with a family history of the disease, may want to consider prophylactic treatment. Family patterns that would be considered positive for breast cancer include (ASPS, 2008):

- Two or more first-degree relatives
- One first-degree and two second or third-degree relatives
- One first-degree relative with cancer prior to age 45 and one other relative
- One first-degree relative and one first-degree relative with ovarian cancer
- Two second or third-degree relatives and one relative with ovarian cancer
- Three or more second or third-degree relatives
- One first-degree relative with bilateral cancer
- Positive BRCA1 or BRCA2
The Society of Surgical Oncology (SSO) updated their position on prophylactic mastectomy in 2007. The position states that BPM in a patient without a diagnosis of breast cancer or evidence of a suspicious breast lesion is one form of risk reduction for the development of breast cancer. Indications for consideration of BPM are best evaluated by a multidisciplinary team which may include a surgeon, medical oncologist, pathologist, as well as a genetic counselor. According to the SSO, clinical presentations that suggest an additional risk of the development of breast cancer and that justify performing a BPM include any of the following:

1. A known mutation of BRCA 1 or BRCA2 or other strongly predisposing breast cancer susceptibility genes.
2. A family history of breast cancer in multiple first-degree relatives and/or multiple successive generations of family members with breast and/or ovarian cancer (familial breast cancer syndrome). Additionally, a family history of multiple family members with bilateral and/or premenopausal and/or male breast cancer may be associated with a familial breast cancer syndrome. Genetic counseling should be strongly considered, although prophylactic surgery is appropriate in women with a family history consistent with genetic predisposition and no demonstrable genetic mutation.
3. High-risk histology: Atypical ductal or lobular hyperplasia, or lobular carcinoma in situ confirmed on biopsy. These changes are especially significant if present in a patient with a strong family history of breast cancer.

The SSO further states that, rarely, BPM may be indicated for a patient without family history or high-risk histology. “Such a patient would exhibit the following characteristics: extremely dense fibroedematous tissue that is difficult to evaluate with standard breast imaging, several prior breast biopsies for clinical and/or mammographic abnormalities, and strong concern about breast cancer risk” (SSO, 2007).

The SSO position statement notes that unilateral prophylactic mastectomy, also referred to as contralateral prophylactic mastectomy (CPM), “may be appropriate in a patient in whom therapeutic mastectomy has previously been performed or is being contemplated for breast cancer.” These patients are at a higher than normal risk for developing contralateral breast cancer. Mastectomy of the contralateral breast may be considered in the following situations (SSO, 2007):

- For risk reduction in patients at high risk for contralateral breast cancer. (See indications as listed above for bilateral prophylactic mastectomy.)
- For patients in whom subsequent surveillance of the contralateral breast would be difficult. This includes patients with clinically and mammographically dense breast tissue, or diffuse indeterminate microcalcifications in the contralateral breast. Stereotactic core biopsy should be performed of any suspicious cluster in this situation to rule out carcinoma. However, diffuse and/or indeterminate calcifications in some situations may make subsequent surveillance difficult. A clinically and mammographically dense breast may also make surveillance difficult.
- For improved symmetry in patients undergoing mastectomy with reconstruction for the index cancer who have a large and/or ptotic contralateral breast, or disproportionately sized contralateral breast. It is difficult to reasonably match these patients’ breasts with reconstructive techniques, and a contralateral mastectomy with reconstruction may be indicated to maintain symmetry. Mastopexy and reduction mammoplasty are alternatives to contralateral mastectomy. In rare situations, a patient having had, or who will undergo, mastectomy without reconstruction may also request a contralateral mastectomy to maintain balance and/or decrease the risk of contralateral breast cancer.

Use Outside of the US

The National Institute for Health and Clinical Excellence (NICE) guideline on the classification and care of women at risk of familial breast cancer states that bilateral risk-reducing mastectomy is appropriate only for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team. Women considering this procedure should have genetic counseling before a decision is made. NICE recommendations also include the following (NICE, 2013):

- Discussion of individual breast cancer risk and its potential reduction by surgery should take place and take into account individual risk factors, including the woman's current age, especially at extremes of age ranges.
• Family history should be verified where no mutation has been identified before bilateral risk-reducing mastectomy.
• Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with bilateral risk-reducing mastectomy.

The National Hereditary Cancer Task Force developed Canadian consensus recommendations to address the clinical management of patients at high risk of HBOC and related cancers. The recommendations are based on current practice in high-risk cancer clinics that provide care for individuals with known BRCA1 or BRCA2 mutations and pertain to surveillance options, risk-reduction strategies (e.g., BPSO, prophylactic mastectomy), and the use of exogenous hormones. The guidelines state that consistent evidence from observational studies suggests that prophylactic mastectomy reduces the risk of breast cancer in women with known BRCA1 or BRCA2. The recommendations pertaining to prophylactic mastectomy include the following (Horsman, et al., 2007):

1. The potential benefits of prophylactic mastectomy as a risk-reduction strategy should be raised with all women with known BRCA1 or BRCA2 mutations.
2. Women considering prophylactic mastectomy should be managed by a multidisciplinary team that includes at least a geneticist/genetic counselor, a breast surgeon, and a plastic surgeon.
3. The surgical technique should aim for maximum removal of breast tissue, including removal of nipple and areola, and possibly also the axillary and subclavian extensions.
4. The possibility that histologically evident breast cancer may be diagnosed as a result of the surgical procedure should be discussed with the patient in advance.
5. Breast reconstruction options should be discussed with the patient in advance.

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• Discussion of individual breast cancer risk and its potential reduction by surgery should take place and take into account individual risk factors, including the woman's current age, especially at extremes of age ranges.
• Family history should be verified where no mutation has been identified before bilateral risk-reducing mastectomy.
• Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with bilateral risk-reducing mastectomy.

Summary
The overall body of evidence in the peer-reviewed medical literature indicates that prophylactic mastectomy is effective in reducing the occurrence of breast cancer for individuals in high-risk categories. It is important that affected individuals receive counseling regarding all available options, in addition to the risks and benefits of the procedure. If the procedure is under consideration as a treatment option, it is imperative that the patient understand that the surgery will not eliminate the risk of developing cancer. Nonetheless, for patients who carry BRCA, p53 or PTEN mutations, prophylactic mastectomy can minimize the additional risk conferred by genetics.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT**</th>
<th>Description</th>
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<td>Codes</td>
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<tr>
<td>19303</td>
<td>Mastectomy, simple, complete</td>
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<td>19304</td>
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References


