Benefit definition: Early and locally advanced breast cancer
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**Disclaimer:**

The breast cancer benefit definition has been developed for the majority of standard patients. These benefits may not be sufficient for outlier patients. Therefore regulation 15h and 15l may be applied for patients who are inadequately managed by the stated benefits. The procedure codes are just an indication of applicable procedure codes, however some significant procedure codes may not have been included. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetist drugs, supportive medication and nursing care. However, these interventions form part of care and are prescribed minimum benefits.
1. Introduction
1.1 The legislation governing the provision of the prescribed minimum benefits (PMBs) are contained in
the regulations enacted under the Medical Schemes Act 131 of 1998. In respect of some of the
diagnosis treatment pairs (DTPs), medical scheme beneficiaries find it difficult to know their
entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting
in a lack of uniformity of benefit entitlements.
1.2 The benefit definition project is coordinated by the Council for Medical Schemes (CMS) and aims to
define the PMB package and to guide the interpretation of the PMB provisions by relevant
stakeholders. The guidelines are based on the available evidence of clinical and cost effectiveness
taking into consideration affordability constraints and financial viability of medical schemes in South
Africa.

2. Scope and purpose
2.1 This is a recommendation for the diagnosis, treatment and care of individuals with early and locally
advanced breast cancer in any clinically appropriate setting as outlined in the Medical Schemes
Act.
2.2 The purpose is to improve clarity in respect of funding decisions by medical schemes, taking into
consideration evidence based medicine, affordability and in some instances cost-effectiveness

3. Epidemiology
3.1 Breast cancer is the most common cancer in women both in the developed and less developed
world. In 2012, 1.7 million women were diagnosed with breast cancer while the prevalence stood at
6.3 million women. According to the World Health Organisation (WHO) Breast cancer was also the
most common cause of cancer death among women with 508 000 deaths in 2011 and 522 000
deaths in 2012. Breast cancer was also the most frequently diagnosed cancer among women in
140 of 184 countries worldwide[1].
3.2 Although breast cancer is thought to be a disease of the developed world, almost 50% of breast
cancer cases and 58% of deaths occur in less developed countries. Incidence rates of breast
cancer vary greatly worldwide from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000
women in Western Europe. In contrast to Eastern Africa, breast cancer was the most commonly
diagnosed cancer and the leading cause of cancer death among women in Southern Africa (9000
cases, 4500 deaths)[2].
3.3 Breast cancer survival rates vary greatly worldwide, ranging from 80% or over in North America, Sweden and Japan to around 60% in middle-income countries and below 40% in low-income countries[3]. The low survival rates in less developed countries can be explained mainly by the lack of early detection programmes, resulting in a high proportion of women presenting with late-stage disease, as well as by the lack of adequate diagnosis and treatment facilities.

3.4 Currently in South Africa 10% of patients with breast cancer present with stage 1 diseases and the remainder presents with 30% each for stages two three and four[4]. According to the South African National Cancer Registry, Breast cancer was the most prevalent cancer amongst women with a lifetime risk of 1:35[5].

### Table 1: Possible ICD 10 codes to identify breast cancer

<table>
<thead>
<tr>
<th>ICD 10</th>
<th>WHO description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z12.3</td>
<td>Special screening examination for neoplasm of breast</td>
<td></td>
</tr>
<tr>
<td>C50.0</td>
<td>Malignant neoplasm, nipple and areola</td>
<td></td>
</tr>
<tr>
<td>C50.1</td>
<td>Malignant neoplasm, central portion of breast</td>
<td></td>
</tr>
<tr>
<td>C50.2</td>
<td>Malignant neoplasm, upper-inner quadrant of breast</td>
<td></td>
</tr>
<tr>
<td>C50.3</td>
<td>Malignant neoplasm, lower-inner quadrant of breast</td>
<td></td>
</tr>
<tr>
<td>C50.4</td>
<td>Malignant neoplasm, upper-outer quadrant of breast</td>
<td></td>
</tr>
<tr>
<td>C50.5</td>
<td>Malignant neoplasm, lower-outer quadrant of breast</td>
<td></td>
</tr>
<tr>
<td>C50.6</td>
<td>Malignant neoplasm, axillary tail of breast</td>
<td></td>
</tr>
<tr>
<td>C50.8</td>
<td>Malignant neoplasm, overlapping lesion of breast</td>
<td></td>
</tr>
<tr>
<td>C50.9</td>
<td>Malignant neoplasm, breast, unspecified</td>
<td></td>
</tr>
<tr>
<td>D05.0</td>
<td>Carcinoma in situ, lobular carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>D05.1</td>
<td>Carcinoma in situ, intraductal carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>D05.7</td>
<td>Carcinoma in situ, other carcinoma in situ of breast</td>
<td></td>
</tr>
<tr>
<td>D05.9</td>
<td>Carcinoma in situ, of breast, unspecified</td>
<td></td>
</tr>
</tbody>
</table>

### 4. Screening

4.1 Current evidence regarding the ability of a mammogram to reduce mortality associated with breast cancer is conflicting. Screening mammogram is therefore not prescribed minimum benefit (PMB) level of care[6]. Clinical breast examination is considered PMB level of care.
5. Diagnostic procedures

Women with signs and symptoms of breast cancer must undergo triple assessment for diagnosis. Triple assessment consist of clinical examination, imaging and pathological assessment [7, 8].

5.1 Clinical assessment:

5.1.1 The diagnostic work-up of early breast cancer starts with assessment of general health status which includes the complete history of the patient, family history relating to cancers, physical examination and biochemical examination.

5.1.2 Clinical examination includes bimanual palpation of the breasts and complete examination of tall systems (bones, liver, brain and lungs) to assess distant metastases.

5.1.3 Blood tests such as liver function test, renal function tests, calcium and phosphates to assess general health and metastatic disease are PMB level of care [7].

5.2 Imaging

Imaging plays a crucial role for classifying and sampling both palpable and non-palpable breast abnormalities, as well as for defining the extent of breast tumours, both locally, loco-regionally, and at distant sites.

5.2.1 Diagnostic mammogram is indicated for most women with positive screening [7, 9].

5.2.2 Ultrasound is indicated for symptomatic younger women (women less than 40 years,) as they have dense breast tissue and high risk of false negatives on mammogram. Ultrasound with mammogram has a better diagnostic value as compared to either test alone in symptomatic women [10-12].

5.2.3 Magnetic resonance Imaging (MRI) of the breast is not routinely recommended. MRI is PMB level of care in women from families not tested or inconclusively tested for BRCA mutation with 20-30% lifetime risk or greater familial breast cancer associated with BRCA mutations, breast implants, lobular cancers and when the findings of conventional imaging are inconclusive [7, 13, 14].

5.2.4 Positron Emission Tomography - Computed Tomography (PET-CT) scan, three dimensional mammographic ultrasound and computed tomography scan are not PMB level of care for diagnosis[15] [7, 16].
5.3 **Pathological assessment**

5.3.1 Ultrasound guided core needle biopsy is the method of choice for diagnosing breast cancer. Core needle biopsy has been shown to reliably distinguish between in-situ and invasive cancers, allow evaluation of more histological, prognostic and predictive factors in breast cancer [17, 18].

5.3.2 Fine needle aspiration (FNA) is indicated as the first-line pathologic investigation for palpable breast lesions. In the case non-palpable lesions, suboptimal sampling and localization remains the main cause of false negative results[19]. Using ultrasound to guide FNA decreases the number of false negative results and increases the sensitivity and specificity of FNA[20, 21].

5.3.3 Excision biopsy is considered a reference standard method of evaluating a suspicious breast lesion. However, the availability of core needle biopsy has limited the role of open surgical biopsy which places the patient at risk of experiencing morbidities. A less invasive method of evaluation of breast lesions is preferred[22].

5.3.4 Frozen section biopsy is not a PMB level of care. Frozen *section biopsy* has been shown to have a limited role in the diagnosis of carcinoma and is not recommended on small lesions (<1cm), where the pathologist believes that freezing will distort subsequent tissue morphology[22]. Current evidence discourages the use of frozen section for evaluation of resection margins that are grossly free of tumour and on a breast excision specimen removed because of mammographic calcifications [21, 22].

5.4 **Evaluation of the Axilla**

5.4.1 Axillary lymph nodal status remains an important prognostic factor because treatment of breast cancer is influenced by the presence of and number of axillary lymph nodes involved.

5.4.2 Sentinel lymph biopsy is a PMB level of care for women with operable breast cancer or ductal carcinoma in situ (DCIS) who will undergo mastectomy [23, 24]. SLNB should not be performed routinely for all patients with an initial diagnosis of DCIS [7, 14, 25].

5.5 **Histological assessment**

5.5.1 Tumour histological type and grading is PMB level of care.
5.5.2 Oestrogen receptor (ER), Progesterone receptor (PR), Ki67 index and human epidermal growth factor receptor 2 (HER2) status is determined on all breast cancers and breast cancer recurrences [26, 27].

5.5.3 Immunohistochemical staining can be performed on the core needle or excision biopsy.

6. Staging and risk assessment
The TNM classification is a universally accepted system that is used to stage breast cancer. TNM staging takes into account the size of the tumour (T), whether the cancer has spread to the lymph glands (lymph nodes) (N), and whether the tumour has spread anywhere else in the body (M – for metastases)[7].

6.1 Current guidelines for the management of women with early breast cancer generally recommend against the routine use of staging imaging to detect asymptomatic distant metastases at the time of diagnosis [7, 28-31].

6.2 Chest x-ray and abdominal ultrasound is PMB level of care for patients with invasive disease.

6.3 Bone scan is considered for patients with clinically positive axillary nodes, large tumours, clinical signs and/or laboratory values suggesting metastases, bone pain to determine the presence of metastases to bone[31]

6.4 Magnetic Resonance Imaging (MRI) is indicated in patients with clinically positive axillary nodes, large tumours, clinical signs and/or laboratory values suggesting metastases to determine metastatic regions[16].

6.5 Computed tomography (CT scan) is considered for patients with clinically positive axillary nodes, large tumours, and clinical signs laboratory values suggesting metastases to determine metastatic regions[16].

6.6 [18F]-fluorodeoxyglucose Positron emission tomography–computed tomography (FDG-PET/CT) is indicated only when conventional methods are not conclusive in determining metastases [32, 33]. This procedure is not a PMB level of care unless distant metastasis is suspected with unequivocal results.

6.7 Post-operative pathological assessment is done according to the primary TNM system and maximum diameter of tumours removed, the total number of lymph nodes removed and number of positive lymph nodes and the extent of metastases in the lymph nodes. Age, tumour stage, ER expression and histological grade are used to estimate the prognosis [9].
Table 2: Diagnostic work-up for breast cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td></td>
</tr>
<tr>
<td>Full blood count</td>
<td>Standard pre-operative assessment for possible bone marrow metastasis</td>
</tr>
<tr>
<td>Liver function tests</td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>Baseline tests to assess possible liver involvement</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
</tr>
<tr>
<td>Alanine transminase</td>
<td></td>
</tr>
<tr>
<td>Aspartate transminase</td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td></td>
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<tr>
<td>Gamma-glutamyl transferase</td>
<td></td>
</tr>
<tr>
<td>Renal function tests</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>Assessment of possible obstructive renal symptoms</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
</tr>
<tr>
<td>Electrolyte</td>
<td></td>
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<tr>
<td>Calcium</td>
<td></td>
</tr>
<tr>
<td>Menopausal</td>
<td></td>
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<tr>
<td>Follicle stimulating hormone</td>
<td></td>
</tr>
<tr>
<td>Luteinising hormone</td>
<td></td>
</tr>
<tr>
<td>Oestradiol</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
</tr>
<tr>
<td>Mammogram</td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Symptomatic younger women (women less than 40 years,) as they have dense breast tissue and high risk of false negatives on mammogram.</td>
</tr>
<tr>
<td>MRI</td>
<td>Not routinely recommended</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Ultrasound guided biopsy</td>
<td></td>
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<tr>
<td>Procedure</td>
<td></td>
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<tr>
<td>---------------------------------</td>
<td></td>
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<tr>
<td>Core needle biopsy</td>
<td></td>
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<tr>
<td>Fine needle aspiration</td>
<td></td>
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<tr>
<td>Pathologic investigation for palpable breast lesions</td>
<td></td>
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<tr>
<td>Axillary lymph node biopsy</td>
<td></td>
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<tr>
<td>Sentinel lymph node biopsy</td>
<td></td>
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<tr>
<td>Lymph node biopsy</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>ER, PR, ki 67 and HER2 determination</td>
<td></td>
</tr>
<tr>
<td>Tumor type and grade</td>
<td></td>
</tr>
</tbody>
</table>

7. Management of localised disease
Management of localised cancer covers surgery, hormonal and radiation therapy. Both Lobular carcinoma in situ (LCIS) and Ductal carcinoma in situ are classified as localised disease. Both conditions are classified as Stage 0 diseases according to the TNM classification method[8].

7.1 Surgery
7.1.1 Surgery for breast cancer in localised disease covers both lumpectomy and mastectomy.
7.1.2 Lumpectomy without lymph node surgery together with or without radiation is indicated in women with DCIS. However, the option of lumpectomy alone should be considered only in cases where the patient and the physician view the individual risks as low[14].
7.1.3 Patients with DCIS and evidence of widespread disease (i.e. disease in 2 or more quadrants) require total mastectomy with or without sentinel node biopsy. Although mastectomy provides maximum local control, long-term cause-specific survival with mastectomy appears to be equivalent to that with excision and whole breast irradiation [8, 34].
7.1.4 Both lumpectomy and mastectomy are PMB level of care for women with early breast cancer.
7.1.5 Prophylactic mastectomy is excluded as PMB level of care.

7.2 Radiation therapy
7.2.1 Radiation therapy is covered in the treatment of patients with DCIS.
7.2.2 Results of clinical trials have shown that radiotherapy after local excision for DCIS, as compared with local excision alone, reduces the overall number of both invasive and non-invasive recurrences in the ipsilateral breast [35-37].

7.2.3 External beam radiation therapy (EBRT) is indicated for localised disease.

7.2.4 There are 3 types of EBRT: conventional radiotherapy, 3D conformal radiation therapy (3D-CRT) and intensity modulated radiotherapy (IMRT).

7.2.5 Supporting evidence has shown that the outcome of conventional therapy versus that of 3D-CRT and IMRT do not differ [38, 39].

7.2.6 Conventional radiotherapy is therefore considered PMB level of care.

7.2.7 The use of partial breast irradiation as standard therapy is not supported because of concerns regarding the long term efficacy of such therapy.

7.3 Hormone therapy.

7.3.1 Currently Tamoxifen, Letrozole, Anastrozole and Exemestane are used in the treatment of early and locally advanced breast cancer.

7.3.2 Tamoxifen is a well-established drug in the treatment of breast cancer and therefore is covered as a PMB level of care.

7.3.3 Aromatase inhibitors (Letrozole, Anastrozole, Exemestane) are PMB level of care.

7.4 Chemotherapy

7.4.1 Chemotherapy is PMB level of care for early breast cancer. The following regimen is PMB level of care:

- CMF
- DC
- FEC 100 or FAC
- AC or FEC/docetaxel
- AC or FEC/weekly paclitaxel

C = cyclophosphamide, M = methotrexate, F = 5-Fluoruracil, D = docetaxel, A = Adriamycin, E = epirubicin
7.5 Surveillance/Follow-up

7.5.1 Follow-up of patients with localised disease includes interval history and physical examinations every 3 to 4 months for the first 2-3 years. This is imperative to monitor tolerance and compliance of hormonal therapy. This is extended to 6 to 12 months for 5 years and then annually as well as yearly diagnostic mammography.

7.5.2 Patients treated with breast-conserving therapy should have follow-up mammography performed 6 to 12 months after completion of breast-conserving radiation therapy.

7.5.3 MRI is not offered routinely post-treatment in patients who have been treated for early invasive breast cancer or DCIS [7, 8, 14].

7.5.4 Mammogram and breast ultrasound are used in the routine post-treatment surveillance of early breast cancer.

8. Management of locally advanced disease

8.1 Patients with locally advanced disease include those with operable (Stage I, IIA, IIB, IIIA: T0 -T3 with a N1-2; N2 with any T1–T3) and inoperable disease at presentation (Stage IIIB: T4a, skin; T4b, chest wall; T4c (a1b) with N1-N2) and those with inflammatory disease (Stage IIIC: N3 with any T, T4d)[8, 40].

8.2 The treatment of locally advanced breast cancer includes a combination of systemic chemotherapy, surgery, hormonal therapy and radiotherapy to optimize the chance of cure[41].

8.3 Neo-Adjuvant Chemotherapy

8.3.1 Neo-Adjuvant Chemotherapy is considered for women with large clinical stage IIA, stage IIB and T3 N1 M0 tumours and Stage IIIB: T4a, skin; T4b, chest wall; T4c (a1b) with N1-N2).

8.3.2 The main goal of neoadjuvant chemotherapy is to enhance surgical options and breast conservation in women with stage 2 or 3 breast cancer who are not candidates for breast conservation [7, 42].

8.3.3 Pre- or postoperative chemotherapy has been shown to have no impact on treatment outcomes on operable cases.

8.3.4 Adjuvant regimens are PMB level of care in the neo-adjuvant setting. The following regimen is PMB level of care:

-- CMF
-- DC
-- FEC 100 or FAC
8.4 Surgery
8.4.1 Mastectomy with axillary lymph node dissection or breast-conserving therapy with lumpectomy, axillary dissection and whole breast irradiation are indicated as a primary breast treatment of women with stage I and stage II breast cancers[8].

8.4.2 Randomised control trail (RCTs) comparing breast conserving surgery with mastectomy found no significant difference in terms of survival or recurrence of disease.

8.4.3 Bilateral mastectomy of the un-diseased breast is not PMB level of care. Bilateral mastectomy is considered in patients with BRCA mutations.

8.5 Surgery to the Axilla
8.5.1 Axillary Lymph Node surgery is indicated if there is an axillary disease. The intention of axillary clearance is to prevent axillary relapse.

8.5.2 Axillary lymph node sampling or clearance may also be used for staging; however axillary lymph node clearance may constitute overtreatment in some patients.

8.6 Adjuvant Chemotherapy
7.5.1 Adjuvant chemotherapy is PMB level of care in patients with operable and inoperable disease [7, 8, 14, 43]. Recommended adjuvant regimens include:

- AC
- FAC
- CMF
- DC
- FEC
- AC or FEC / docetaxel (sequential)
- AC or FEC / paclitaxel (sequential)

7.5.2 Supporting care for chemotherapy induced nausea and vomiting is PMB level of care.
8.7 Hormonal therapy

8.7.1 Patients with invasive breast cancers that are ER- or PR- positive are considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether adjuvant chemotherapy is to be administered. [8, 14].

8.7.2 Tamoxifen is indicated for 5 years in patients with non-metastatic hormone receptor positive breast cancer.

8.7.3 Aromatase inhibitors are PMB level of care for the duration of hormonal therapy.

8.7.4 Luteinizing hormone-releasing hormone (LHRH) agonist are indicated for premenopausal with tamoxifen contraindication or where aromatase inhibitors are indicated.

Table 5: Hormonal therapy for locally advanced disease

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>Adjuvant Tamoxifen for 5 years in patients with non-metastatic hormone receptor positive breast cancer</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Postmenopausal women with ER-positive early invasive breast cancer</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Postmenopausal women with ER-positive early invasive breast cancer</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Postmenopausal women with ER-positive early invasive breast cancer</td>
</tr>
<tr>
<td>LHRH Agonist + Aromatase Inhibitors</td>
<td>Premenopausal patient where aromatase inhibitors is indicated</td>
</tr>
</tbody>
</table>

8.8 Biological therapy

8.8.1 Biological therapy is not covered as a PMB level of care.

8.9 Radiation therapy

8.9.1 After mastectomy and axillary dissection, radiotherapy has been shown to reduce both recurrence and breast cancer mortality in women with one to three positive lymph nodes in clinical trials[44, 45].

8.9.2 External beam radiation therapy is indicated for localised disease. There are 3 types of EBRT: conventional radiotherapy, 3d conformal radiation therapy (3d-CRT) and intensity modulated radiotherapy.

8.9.3 The use of partial breast irradiation as standard therapy is not a PMB level of care because of concerns regarding the long term efficacy of such therapy.

8.9.4 Supporting evidence has shown that the outcome of conventional therapy versus that of 3d-CRT and IMRT do not differ.
8.9.5 Conventional radiotherapy is therefore covered as a PMB level of care.

8.10 **Follow up**

8.10.1 The purpose of long term follow up is to monitor disease progression, to assess and encourage adherence to adjuvant endocrine therapy, to encourage active lifestyle and maintenance of ideal body weight (20-25 BMI) and to manage chemotherapeutic adverse events.

8.10.2 Follow-up of patients with locally advanced disease includes interval history and physical examinations every 3 to 4 months for the first 2-3 years. This is imperative to monitor tolerance and compliance of hormonal therapy. This is extended to 6 to 12 months up to 5 years and then annually as well as yearly diagnostic mammography.

8.10.3 Mammography every 12 months is PMB level of care.

8.10.4 Annual gynaecologic assessment every 12 months if uterus present is PMB level of care for women on Tamoxifen for the duration of Tamoxifen use.

8.10.5 Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment are monitored for bone health with a bone mineral density determination at baseline and periodically thereafter.

8.10.6 Bisphosphonates are PMB level of care for patients with reduced bone mineral density.

9. **Breast Replacement options**

9.1 Breast replacement option for the affected breast is a PMB level of care for women who have undergone mastectomy. Revision reconstruction is a PMB level of care where it is clinically indicated.

9.2 An external prosthesis is a PMB level of care for women who decide that breast reconstruction isn't right for them but still want a breast shape.

9.3 Implants and/or flaps are PMB level of care for women who have undergone mastectomy. Deep Inferior Epigastric Perforators (DIEP) flap is not covered as a PMB level of care.

9.4 Reconstruction of the unaffected breast is not a PMB level of care.
10. Reference
