Policy Statement

The use of positron emission mammography (PEM) is considered **investigational** for all indications.

Policy Guidelines

Coding

There are no specific CPT codes for positron emission mammography.

The following CPT/HCPCS codes may be used to describe PEM:

- **78811**: Positron emission tomography (PET) imaging; limited area (e.g., chest, head/neck)
- **78999**: Unlisted miscellaneous procedure, diagnostic nuclear medicine
- **G0235**: PET imaging, any site, not otherwise specified

Description

Positron emission mammography (PEM) is a form of positron emission tomography that uses high-resolution, mini-camera detection technology for imaging the breast. As with positron emission tomography, PEM provides functional rather than anatomic information about the breast. PEM has been studied primarily for use in presurgical planning and evaluation of breast lesions.

Related Policies

- Digital Breast Tomosynthesis
- Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer
- Oncologic Applications of Positron Emission Tomography Scanning
- Scintimammography and Gamma Imaging of the Breast and Axilla

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 2003, the PEM 2400 PET Scanner (PEM Technologies) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for “medical purposes to image and measure the distribution of injected positron emitting radiopharmaceuticals in human beings for
the purpose of determining various metabolic and physiologic functions within the human body.”14

In 2009, the Naviscan PEM Flex™ Solo II™ High Resolution PET Scanner (Naviscan) was cleared for marketing by the FDA through the 510(k) process for the same indication. The PEM 2400 PET Scanner was the predicate device. The newer device has been described by the manufacturer as “a high spatial resolution, small field-of-view PET imaging system specifically developed for close-range, spot, ie, limited field, imaging.”

In 2013, Naviscan was acquired by Compañía Mexicana de Radiología SA,15 which currently markets the Naviscan Solo II™ Breast PET Scanner in the United States (CMR Naviscan). FDA product code: KPS.

Rationale

Background

Positron Emission Mammography

Positron emission mammography (PEM) is a form of positron emission tomography (PET) that uses a high-resolution, mini-camera detection technology for imaging the breast. As with PET, a radiotracer (usually fluorine 18 fluorodeoxyglucose) is administered, and the camera is used to provide a higher resolution image of a limited section of the body than would be achievable with fluorine 18 fluorodeoxyglucose PET. Gentle compression is used, and the detector(s) are mounted directly on the compression paddle(s).1-3

PEM was developed to overcome the limitations of PET for detecting breast cancer tumors. Patients are usually supine for PET procedures; further, breast tissue may spread over the chest wall, making it potentially difficult to differentiate breast lesions from other organs that take up the radiotracer. PET’s resolution is generally limited to approximately 5 mm, which may not detect early breast cancer tumors.4 PEM allows for the detection of lesions as small as 2 to 3 mm and creates images that are more easily compared with mammography because they are acquired in the same position.2,5 Three-dimensional reconstruction of PEM images also is possible. As with PET, PEM provides functional rather than anatomic information about the breast.1-3 In PEM studies, exclusion criteria have included some patients with diabetes (e.g., Berg et al [2011, 2012]6,7).

Radiation Dose Associated with PEM

The label-recommended dose of fluorine 18 fluorodeoxyglucose for PEM is 370 MBq (10 mCi). Hendrick (2010) calculated mean glandular doses, and from the doses was able to determine lifetime attributable risk (LAR) of cancer for film mammography, digital mammography, breast-specific gamma imaging (BSGI), and PEM.8 The author used BEIR VII Group risk estimates9 to gauge the risks of radiation-induced cancer incidence and mortality from breast imaging studies. Estimated LAR of cancer for a patient with an average-sized compressed breast during mammography of 5.3 cm (risks would be higher for larger breasts) for a single breast procedure at age 40 years was calculated as:

- 5 per 100,000 for digital mammography (breast cancer only)
- 7 per 100,000 for screen-film mammography (breast cancer only)
- 55 to 82 per 100,000 for BSGI (depending on the dose of technetium 99m sestamibi)
- 75 per 100,000 for PEM

The corresponding LAR of cancer mortality at age 40 years was:

- 1.3 per 100,000 for digital mammography (breast cancer only)
- 1.7 per 100,000 for screen-film mammography (breast cancer only)
- 26 to 39 per 100,000 for BSGI
- 31 per 100,000 for PEM
A major difference in the impact of radiation between mammography and BSGI or PEM is that in mammography radiation dose is limited to the breast; whereas with BSGI and PEM, all organs are irradiated. Furthermore, as one ages, the risk of cancer induction from radiation exposure decreases more rapidly for the breast than for other radiosensitive organs. Organs at highest risk for cancer are the bladder with PEM and the colon with BSGI; these cancers, along with lung cancer, are also less curable than breast cancer. Thus, the distribution of radiation throughout the body adds to the risks associated with BSGI and PEM. Hendrick concluded that:

“... BSGI and PEM are not good candidate procedures for breast cancer screening because of the associated higher risks for cancer induction per study compared with the risks associated with existing modalities such as mammography, breast US [ultrasound], and breast MR [magnetic resonance] imaging. The benefit-to-risk ratio for BSGI and PEM may be different in women known to have breast cancer, in whom additional information about the extent of disease may better guide treatment.”

O’Connor et al (2010) estimated the LAR of cancer and cancer mortality from the use of digital mammography, screen-film mammography, PEM, and molecular breast imaging. Only results for digital mammography and PEM are reported here. The authors concluded that, in a group of 100,000 women at age 80 years, a single digital mammogram at age 40 years would induce 4.7 cancers with 1.0 cancer deaths; 2.2 cancers with 0.5 cancer deaths for a mammogram at age 50; 0.9 cancers with 0.2 cancer deaths for a mammogram at age 60; and 0.2 cancers with 0.0 cancer deaths for a mammogram at age 70. Comparable numbers for PEM would be 36 cancers and 17 cancer deaths for PEM at age 40; 30 cancers and 15 cancer deaths for PEM at age 50; 22 cancers and 12 cancer deaths for PEM at age 60; and 9.5 cancers and 5.2 cancer deaths for PEM at age 70. The authors also analyzed the cumulative effect of annual screening between the ages of 40 and 80, as well as between the ages of 50 and 80. For women at age 80 who were screened annually from the ages of 40 to 80, digital mammography would induce 56 cancers with 15 cancer deaths; for PEM, the analogous numbers were 800 cancers and 408 cancer deaths. For women at age 80 who were screened annually from the ages of 50 to 80, digital mammography would induce 21 cancers with 6 cancer deaths; for PEM, the analogous numbers were 442 cancers and 248 cancer deaths. However, background radiation from age 0 to 80 is estimated to induce 2174 cancers and 1011 cancer deaths.

These calculations, like all estimated health effects of radiation exposure, are based on several assumptions. When comparing digital mammography with PEM, 2 conclusions become clear: Many more cancers are induced by PEM than by digital mammography; and for both modalities, adding annual screening from age 40 to 49 roughly doubles the number of induced cancers. In a benefit-risk calculation performed for digital mammography but not for PEM, O’Connor et al (2010) nevertheless reported that the benefit-risk ratio of annual screening is still approximately 3 to 1 for women in their 40s, although it is much higher for women age 50 and older. Like Hendrick, the authors concluded that “if molecular imaging techniques [including PEM] are to be of value in screening for breast cancer, then the administered doses need to be substantially reduced to better match the effective doses of mammography.”

The American College of Radiology has assigned a relative radiation level (effective dose) of 10 to 30 mSv to PEM. The College has also stated that, because of radiation dose, PEM and BSGI in their present form are not indicated for screening.

Because the use of BSGI and molecular breast imaging have been proposed for women at high risk of breast cancer, it should be noted there is controversy and speculation whether some women (e.g., those with BRCA variants) have heightened radiosensitivity. If women with BRCA variants are more radiosensitive than the general population, the previous estimates may underestimate the risks they face from breast imaging with ionizing radiation (i.e., mammography, BSGI, molecular breast imaging, PEM, single-photon emission computed tomography, breast-specific computed tomography, and tomosynthesis; ultrasound and magnetic resonance imaging do not use radiation). More research will be needed to resolve this issue. Also, risks associated with radiation exposure will be greater for women at high risk of.
breast cancer (regardless of whether they are more radiosensitive) because they start screening at a younger age when the risks associated with radiation exposure are increased.

**Literature Review**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

The highest quality evidence, summarized in this section, focuses on the diagnostic accuracy of positron emission mammography (PEM) compared with other methods, with histopathology as a reference standard. No randomized controlled trials (RCTs) beginning with the use of PEM and following up on clinical outcomes were found.

**PEM as a Screening Test for Breast Cancer**

**Clinical Context and Test Purpose**

The purpose of PEM in patients who undergo breast cancer screening is to inform a decision whether to proceed to further diagnostic testing.

The question addressed in this evidence review is: Does the use of PEM improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest is women who are at average or high risk of breast cancer and scheduled for routine screening.

**Interventions**

The test being considered is PEM.

**Comparators**

The following tests are currently being used to make decisions about managing breast screening: mammography, ultrasound and magnetic resonance imaging (MRI).

**Outcomes**

The general outcomes of interest are diagnostic accuracy measures including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Additional outcomes are the occurrence of breast cancer and breast cancer-related survival.

Beneficial outcomes of a true-positive test result are early diagnosis and treatment. Beneficial outcomes of a true-negative test result are avoidance of additional testing, including biopsy.

The harmful outcome of a false-positive test is further testing including biopsy. Harmful outcomes of a false-negative test are a late diagnosis of breast cancer leading to a requirement for adjunctive treatment with chemotherapy or radiotherapy and poorer outcomes.

Direct harms of the test are from radiation exposure. The American College of Radiology has assigned a relative radiation level (effective dose) of 10 to 30 mSv to PEM, which the College considers too high for a screening test.11
Timing
The reference standard is histopathology or at least 1 year of follow-up for women with negative findings. Follow-up over 10 to 20 years would be needed to monitor for the occurrence of breast cancer, breast cancer-related survival, and overall survival.

Setting
PEM is administered in a dedicated breast imaging unit.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Yamamoto et al (2016) retrospectively reviewed the opportunistic use of PEM for breast cancer screening in 265 women with breast symptoms. Images were evaluated by agreement between 2 experienced readers who had access to clinical information. The maximum PEM uptake value (PUVmax) was calculated by tissue concentration (mCi/g) × body weight (g)/injected fluorine 18 fluorodeoxyglucose (FDG) dose (in millicuries [mCi]). Using a threshold of 1.97, 22 (8.3%) women had abnormal uptake and were recalled. Six (2.3%) cancers were found by PEM. Although higher than the usual detection rate with mammography and physical examination, this was not a general screening population. Sensitivity (76%) and specificity (85%) were calculated by clinical follow-up for this population.

A few studies have reported mixed results whether the sensitivity of PEM is affected by breast tissue density and how PEM compares with MRI of the breast.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing the clinical utility of PEM as a screening test for breast cancer.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of PEM as a screening test for breast cancer has not been established, a chain of evidence supporting PEM’s clinical utility cannot be constructed.

Section Summary: PEM as a Screening Test for Breast Cancer
A single study was identified that evaluated the use of PEM for breast cancer screening, which is insufficient evidence on which to draw conclusions.
PEM for Presurgical Evaluation of Clinically Localized Breast Cancer

Clinical Context and Test Purpose
The purpose of PEM in patients who have a malignant breast lesion is to inform the surgical approach. Testing seeks to identify if there are multifocal or contralateral cancerous lesions that may lead to different treatment recommendations such as mastectomy instead of breast-conserving surgery.

The question addressed in this evidence review is: Does the use of PEM improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is women who have clinically localized breast cancer.

Interventions
The test being considered is PEM.

Comparators
The following practices are currently being used to make decisions about the presurgical evaluation of breast cancer: mammography and breast MRI are established imaging modalities for presurgical evaluation. Histopathology of an identified lesion is the criterion standard for evaluating the test.

Outcomes
The general outcomes of interest are diagnostic accuracy measures including sensitivity, specificity, PPV, and NPV. Test sensitivity is important for presurgical clinical decision making.

Beneficial outcomes of a true-positive test include successful removal of a cancerous lesion. Beneficial outcomes of a true-negative test are avoidance of an unnecessary biopsy.

Harmful outcomes of a false-negative test result are missing lesions, leading to more advanced cancer and reduced survival. A false-positive test is less critical since biopsy confirmation would resolve lesion status as part of developing a cancer management recommendation.

Direct harms of the test are from radiation exposure, which has been reported by the American College of Radiology to be high at 10 to 30 mSv.

Timing
Follow-up over 10 to 20 years would be needed to monitor for the occurrence of breast cancer and breast cancer-related survival.

Setting
PEM is administered in a dedicated breast imaging unit.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
Prospective Studies

Schilling et al (2011) conducted a single-site, prospective study comparing PEM with MRI (1.5 tesla) for presurgical planning in 182 patients. The performances of PEM, MRI, and whole-body positron emission tomography (WBPET) were compared with final surgical histopathology in women with newly diagnosed, biopsy-proven breast cancer. For PEM and WB PET (performed consecutively), median FDG dose was 432.9 MBq (equivalent to 11.7 mCi); 4-to-6 hour fasting glucose less than 7.8 mmol/L was required for study entry. One of the 6 readers evaluated PEM, radiographic mammography, and magnetic resonance images with access to conventional imaging (mammography or ultrasound) results “but without influence of the alternative (PEM or MRI) imaging modality”; WBPET images were interpreted by a nuclear medicine physician. Almost half (46%) of lesions were clinically palpable. On pathology, 78% of patients had invasive disease, 21% had ductal carcinoma in situ (DCIS), and 2% had Paget disease. For index lesions, both PEM and MRI had a sensitivity of 93% (p=NS), which was greater than the sensitivity of WBPET (68% p<0.001). The specificity was not reported because only malignant index lesions were analyzed. The sensitivity of PEM and MRI was not affected by breast density, menopausal status, or use of hormone replacement therapy. Correlation between tumor size on histopathology vs size on PEM or MRI was the same (r=0.61). Twelve lesions were missed on both PEM and MRI; three were not in the PEM field-of-view due to patient positioning. For 67 additional ipsilateral lesions detected (40 malignancies), the sensitivity of PEM and MRI was 85% and 98% (p=0.074), respectively; and the specificity of PEM and MRI was 74% and 48% (p=0.096), respectively. Further investigation is needed to determine whether these are 2 points along the same operating curve (i.e., whether PEM is being read to emphasize specificity compared with MRI).

Berg et al (2011) compared PEM with MRI in a multicenter study of 388 women who had newly diagnosed breast lesions confirmed with core-needle or vacuum-assisted biopsy. The study was funded in part by the manufacturer and the National Institutes of Health. Mean FDG dose with PEM was 10.9 mCi, and the mean blood glucose level was 91 g/dL. PEM and MRI were read by different investigators; some but not all readers were blinded to results of the other test. PEM results with a Breast Imaging-Reporting and Data System (BI RADS) score of 4a or higher or a score of 3 with a recommendation for biopsy were considered positive. Negative cases included those with negative pathology or follow-up of at least 6 months with no suspicious change. After surgery, 386 lesion sites in 370 breasts were confirmed. Among 386 surgically confirmed lesion sites, there was no statistically significant difference in the sensitivity of PEM (93%) and MRI (89%) when only tumor sites were included (p=0.79). When tumors and biopsy sites were visualized, MRI had higher sensitivity (98%) than PEM (95% p=0.004). Of 388 enrolled women, 82 (21%) had additional tumor foci after study entry. Sensitivity for identifying breasts with these lesions was 60% for MRI and 51% for PEM. Of 82 additional lesions, 21 (26%) were detected only with MRI, 14 (17%) only with PEM (p=0.31), and 7 (8.5%) only with conventional imaging. Adding PEM to MRI increased sensitivity from 60% to 72% (p<0.01). Twelve women who had additional foci in the breast with the primary tumor were not identified by any of the imaging techniques. Among women with an index tumor and no additional lesions in the ipsilateral breast, PEM (91%) was more specific than MRI (86% p=0.032). The statistical difference between PEM and MRI area under the receiver operating characteristic curve did not differ significantly. As in the study by Schilling et al, the question arises whether differences in sensitivity and specificity between the 2 tests arose from selecting different operating points along the receiver operating characteristic curve.

Of 116 malignant lesions unknown at study entry, 53% were reported as suspicious on MRI vs 41% on PEM (p=0.04). There was no difference between PEM and MRI in detecting DCIS in this study (41% vs 39% p=0.83). Adding PEM to MRI would increase the sensitivity for detecting DCIS from 39% (MRI alone) to 57% (combined; p=0.001); another 7 DCIS foci were seen only on conventional imaging. MRI was more sensitive than PEM in detecting invasive cancer (64% vs 41% p<0.004), but the 2 combined had a higher sensitivity than MRI alone (73% vs 64% p=0.025). MRI was more sensitive than PEM in dense breasts (57% vs 37% p=0.031).
In a second report from the Berg (2012) study (discussed above), the respective performance of PEM and MRI for detecting lesions in the contralateral breast were compared. In this case, readers were blinded to results of the other test but knew the results of conventional imaging and pathology from pre-study biopsies. After recording results for a single modality, readers then assessed results across all modalities. The final patient sample size was 367; 9 patients were excluded because the highest scored lesion was a BIRADS 3 (probably benign) based on all imaging. No follow-up or histopathology was performed. The contralateral breast could not be assessed in 12 women (e.g., due to prior mastectomy or lumpectomy and radiotherapy).

Fifteen (4%) of the 367 participants had contralateral cancer. PEM detected cancer in 3 of these women and MRI in 14. The sensitivity of PEM and MRI was 20% and 93%, respectively (p<0.001), and the specificity was 95% and 90%, respectively (p=0.002). The area under the receiver operating characteristic curve was 68% for PEM and 96% for MRI (p<0.001). Among women undergoing biopsies, the PPV did not differ statistically between modalities (21% for PEM vs 28% for MRI; p=0.58). There were more benign biopsies based on MRI results (39 biopsies in 34/367 women) than on PEM results (11 biopsies in 11/367 women; p<0.001). The authors discussed possible improvements in interpreting PEM, based in part on results of having the lead investigators reread the PEM images. The authors determined that 7 of 12 false-negative PEM results were due to investigator error. The error could only be confirmed through further study. The authors also noted that a substantial proportion of contralateral lesions could be effectively treated by chemotherapy and that PEM cannot optimally evaluate the extreme posterior breast. Additional articles have assessed the same study, focusing on identifying malignant characteristics on PEM and on training and evaluating readers of PEM.

In an early 4-site clinical study, Tafra et al (2005) imaged 94 women with suspected (n=50) or proven (n=44) breast cancer with PEM. Additional study details are reviewed in the next section. Of note, PEM correctly detected multifocality in 64% of 31 patients evaluated for it and correctly predicted its absence in 17 patients.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing the clinical utility of PEM as a presurgical test to localize breast lesions.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of PEM as a presurgical test to localize breast lesions has not been established, the chain of evidence supporting the clinical utility of this test cannot be constructed.

Section Summary: PEM for Presurgical Evaluation of Clinically Localized Breast Cancer
Results for diagnostic performance of PEM in the presurgical evaluation of clinically localized breast cancer from 3 multicenter and 1 single-site studies have reported that PEM may be able to detect ipsilateral cancer lesions or lesions in the contralateral breast with moderate sensitivity, but usually low specificity. Studies that compared PEM with MRI, which may be used in this
clinical context, generally found that MRI was more sensitive than PEM. Test sensitivity is important for presurgical clinical decision making since additional testing seeks to identify if there are multifocal or contralateral cancerous lesions that may lead to different treatment such as mastectomy instead of breast-conserving surgery. Specificity is less critical because biopsy confirmation would resolve lesion status as part of developing a cancer management recommendation.

**PEM for a Suspicious Breast Lesion on Conventional Breast Cancer Evaluation**

**Clinical Context and Test Purpose**
The purpose of PEM in patients who have a suspicious breast lesion is to inform a decision of whether to proceed with a biopsy. Suspicious breast lesions on conventional breast cancer evaluation would generally be recommended for biopsy.

The question addressed in this evidence review is: Does the use of PEM improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is women who have localized suspicious breast lesion identified during the conventional evaluation.

**Interventions**
The test being considered is PEM.

**Comparators**
The following practices are currently being used to make decisions about managing suspicious breast lesions breast cancer: biopsy, diagnostic mammography views, and MRI. Biopsy with histopathology of identified lesions is the criterion standard for evaluating the test.

**Outcomes**
Outcomes of interest are diagnostic validity (sensitivity, specificity, PPV, and NPV).

The beneficial outcome of a true-negative test is to avoid biopsy by downgrading suspicion of malignancy. The beneficial outcome of a true-positive test is appropriate biopsy and treatment.

Harmful outcomes of a false-negative result include failure to proceed to diagnosis and treatment. Harmful outcomes of a false-positive test are an unnecessary biopsy.

Direct harms of the test are from radiation exposure, which has been reported by the American College of Radiology to be high at 10 to 30 mSv.

**Timing**
Follow-up over at least 1 year would be needed to monitor suspicious breast findings on mammography that are not biopsied. A clinical pathway for repeat use of PEM has not been identified. Follow-up over 10 to 20 years would be needed to monitor for the occurrence of breast cancer and breast cancer-related survival.

**Setting**
PEM is administered in a dedicated breast imaging unit.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Caldarella et al (2014) conducted a meta-analysis of PEM studies in women with newly discovered breast lesions suspicious for malignancy. Literature was searched through January 2013. Eight studies (total N=873 patients) of 10 or more patients (range, 16-388 patients) that used the histologic review as the criterion standard, including 3 studies described in detail next, were included. The pooled sensitivity and specificity were 85% (95% confidence interval, 83% to 88%; I²=74%) and 79% (95% confidence interval, 74% to 83%; I²=63%), respectively. The pooled PPV and NPV were 92% and 64%, respectively. Comparator arms were not pooled. Other limitations of selected studies included substantial statistical heterogeneity and lack of blinding of both PEM and histopathology readers.

In a 4-site clinical study, Tafra et al (2005) imaged 94 women who had suspected (n=50) or proven (n=44) breast cancer with PEM. The median dose of FDG was 13 mCi; median patient age was 57 years, and median tumor size was 22 mm on pathology review. Seventy-seven percent of primary lesions were nonpalpable. Cases deemed “unevaluable” were excluded (not reported). Eight readers had access to mammography and clinical breast examination results as well as clinical information, but no information on surgical planning or outcomes. At least 2 readers evaluated each case in random order. The performance of PEM in this study is listed next; results are detailed to illustrate potential uses of PEM:

- A BI-RADS category of 4b, 4c, or 5 (probably malignant) was assigned to 39 (89%) of 44 pathologically confirmed breast cancers. Five missed lesions ranged in size from 1 to 10 mm, and 4 were low grade.
- Extensive DCIS was predicted in 3 cases and confirmed to be malignant; the tumors were not detected by other imaging modalities.
- Among 44 patients with proven breast cancer, 5 incidental benign lesions were correctly classified, and 4 of 5 incidental malignant tumors were detected, 3 of which were not detected with other imaging modalities (it was not evident whether MRI was performed on these specific patients).
- PEM correctly detected multifocality in 64% of 31 patients evaluated for it and correctly predicted its absence in 17 patients.
- PEM correctly predicted 6 of 8 patients undergoing partial mastectomy who had positive margins and 11 of 11 who had negative margins.

Berg et al (2006) published an evaluation of PEM in 77 patients. Patients with type 1 or type 2 diabetes were excluded because FDG is glucose-based, and diabetic patients must have well-controlled glucose for the test to work. Median age was 53 years. Of 77 patients, 33 had suspicious findings on core biopsy before PEM, 38 had abnormalities on radiographic mammography, and 6 had suspicious findings on clinical breast exam. Five women had personal histories of breast cancer, one of whom had reconstructive surgery. Readers had access to mammographic and clinical findings because it was assumed they would in clinical practice. The median dose of FDG was 12 mCi (range, 8.2-21.5 mCi). Forty-two of 77 cases were malignant, and 2 had atypical ductal hyperplasia. Sensitivity and specificity rates for PEM were 93% and 85%, respectively, for index lesions, and 90% and 86%, respectively, for index and incidental lesions. These values were similar or higher if lesions were clearly benign on conventional imaging. Adding PEM to radiographic mammography and ultrasound (when available) yielded sensitivity and specificity of 98% and 41%, respectively. (The specificity of PEM combined with conventional imaging was lower than PEM alone due to a large number of false-positive lesions prompted by conventional imaging.)

Muller et al (2016) evaluated the diagnostic accuracy of PEM using PUVmax as a threshold (instead of a ratio) in 108 patients with 151 suspected lesions. FDG dose was 3.5 MBq/kg of
body weight, with a mean of 231.8 MBq. PUV in lesions, tumors, benign lesions, and healthy tissue on the contralateral side were assessed. The biopsy could be performed at the same time as the PEM using the same machine, and suspected carcinoma was compared with histopathology. The mean PUVmax for malignant tumors was 3.78, and the mean PUVmax for normal breast tissue was 1.17 (p<0.001). Using a PUV of more than 1.9 as a threshold, 31 (20.5%) of 151 lesions were identified as malignant and underwent biopsy. Histopathologic evaluation showed 26 malignant (true-positive) and 5 benign (false-positive) lesions. No false-negative lesions were reported, although only lesions suspected of carcinoma by PEM underwent histopathologic analysis. Patients not biopsied had a clinical follow-up for 3 years. The threshold of 1.9 was found via receiver operating characteristic analysis. At this threshold, PEM was reported to have 100% sensitivity and 96% specificity. Based on these positive results, the German health administration has funded a follow-up multicenter study.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing the clinical utility of PEM as a test to identify suspicious breast lesions.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of PEM as a presurgical test to identify suspicious lesions has not been established, the chain of evidence supporting the clinical utility of this test cannot be constructed.

**Section Summary: PEM for Suspicious Breast Lesion on Conventional Breast Cancer Evaluation**
Results for diagnostic performance of PEM in the evaluation of suspicious breast lesions on conventional breast cancer evaluation are available from a meta-analysis as well as 3 other studies. Pooled results from the meta-analysis showed moderate sensitivity and specificity and reasonably high PPV given the population of suspicious lesions. However, the NPV was relatively low (64%). Because suspicious breast lesions on conventional breast cancer evaluation would generally be recommended for biopsy, the proposed clinical use for PEM would be to avoid biopsy by ruling out malignancy. The diagnostic performance from the available studies and low NPV in this population would not support clinical utility in these patients.

**Other Indications**
No full-length, published studies were identified that addressed management of breast cancer and evaluation for breast cancer recurrence.

**Summary of Evidence**
For individuals who are being screened for breast cancer, have clinically localized breast cancer undergoing presurgical evaluation, or have a suspicious breast lesion on conventional breast cancer evaluation who receive PEM, the evidence includes prospective and retrospective studies as well as a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. For each indication, it has not been demonstrated that PEM provides better diagnostic accuracy than the relevant
comparators nor has PEM been shown to provide clinical utility. In addition, without demonstrated advantages in clinical utility, the relatively high radiation dosage associated with PEM does not favor its use given that alternative tests deliver lower doses. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

American College of Radiology
The American College of Radiology has included positron emission mammography (PEM) in its criteria on breast screening.11 PEM was rated as “usually not appropriate” for screening women at average or high risk for breast cancer. The College has also assigned a relative radiation level (effective dose) of 10 to 30 mSv to PEM and stated that PEM is limited “by radiation dose and lack of evidence in large screening population”.

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines for breast cancer screening and diagnosis (v.2.2018) do not include PEM.24

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for PEM have been identified.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02770586</td>
<td>Comparison of Positron Emission Mammography and Contrast-enhanced Breast MRI in Women with a High Suspicion of Breast Cancer</td>
<td>150</td>
<td>Aug 2019</td>
</tr>
<tr>
<td>NCT03520218</td>
<td>A Pilot Study to Evaluate Low-Dose Positron Emission Mammography Imaging in Visualization and Characterization of Suspicious Breast Abnormalities</td>
<td>100</td>
<td>Jun 2020</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01241721</td>
<td>Clinical Value of Pre-Surgery Positron Emission Mammography (PEM) in Patients with Newly Diagnosed Breast Cancer</td>
<td>34</td>
<td>Apr 2016 (completed)</td>
</tr>
<tr>
<td>NCT00896649</td>
<td>Impact of Dedicated Breast Positron Emission Mammography vs. Conventional Two-View Digital Mammography on Recall Rates and Cancer Detection as a Screening Examination in Underserved Women</td>
<td>260</td>
<td>Jan 2017 (completed)</td>
</tr>
<tr>
<td>NCT01864083a</td>
<td>FACBC PET and PEM as a Staging Tool and Indicator of Therapeutic Response in Breast Cancer Patients</td>
<td>30</td>
<td>Aug 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

References


**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>78811</td>
<td>Positron emission tomography (PET) imaging; limited area (e.g., chest, head/neck)</td>
</tr>
<tr>
<td></td>
<td>78999</td>
<td>Unlisted miscellaneous procedure, diagnostic nuclear medicine</td>
</tr>
<tr>
<td>HCPCS</td>
<td>G0235</td>
<td>PET imaging, any site, not otherwise specified</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td>PET imaging, any site, not otherwise specified</td>
</tr>
</tbody>
</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/27/2013</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/30/2015</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>11/01/2016</td>
<td>Policy title change from Positron Emission Mammography (PEM) Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>11/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>11/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>


Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.