Positron Emission Mammography (PEM)

Policy # 00285
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Scintimammography and Gamma Imaging of the Breast and Axilla is addressed separately in medical policy 00438.

Note: Positron Emission Tomography (PET) Oncology Applications is addressed separately in medical policy 00105.

Note: Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer is addressed separately in medical policy 00084.

Note: Digital Breast Tomosynthesis is addressed separately in medical policy 00293.

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

Based on review of available data, the Company considers the use of positron emission mammography (PEM) for all indications to be **investigational.***

Background/Overview

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 [FDG]) 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 FDG-PET. Gentle compression is used, and the detector(s) are mounted directly on the compression paddle(s). 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. 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. Three-dimensional reconstruction of PEM images also is possible. As with PET, PEM provides functional rather than anatomic information about the breast. In PEM studies, exclusion criteria included some patients with diabetes (e.g., Berg et al [2011, 2012]).

Radiation Dose Associated With PEM

The label-recommended dose of FDG 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. The author used

BEIR VII Group risk estimates to gauge the risks of radiation-induced cancer incidence and mortality from breast imaging studies. Estimated LAR of cancer for a patient with 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 is:

- 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); and
- 75 per 100,000 for PEM.

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

- 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; and
- 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:

> "results reported herein indicate 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 (MBI). Only results for digital mammography and PEM are reported here. The study 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 ages 40 and 80, as well as between ages 50 and 80. For women at age 80 who

were screened annually from ages 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 ages 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 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 MBI have been proposed for women at high risk of breast cancer, it should be noted that 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, MBI, PEM, single-photon emission computed tomography, breast-specific computed tomography, and tomosynthesis; US and magnetic resonance imaging (MRI) 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 2003, the PEM 2400 PET Scanner (PEM Technologies, Ridgefield, NJ) was cleared for marketing by the U.S. FDA through the 510(k) process. 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."

In 2009, the Naviscan PEM Flex™‡ Solo II™‡ High Resolution PET Scanner (Naviscan, San Diego, CA) was cleared for marketing by 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, i.e., limited field, imaging."

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

Centers for Medicare and Medicaid Services (CMS)
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.

Rationale/Source

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

PEM AS A SCREENING TEST FOR BREAST CANCER
In 2016, Yamamoto et al 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 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.

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
Schilling et al (2011) conducted a single-site, prospective study comparing PEM and 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 WBPET (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 6 readers evaluated PEM, radiographic mammography, and MR images with access to conventional imaging (mammography or US) 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). Additional larger studies are warranted.

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 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 (AUROC) 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 ROC 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 article based on 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 results of conventional imaging and pathology from prestudy biopsies. After recording results for a single modality, readers then assessed results across all modalities. The final patient sample size was 367; and 9 patients were excluded because the highest scored lesion was a BI-RADS 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 ($p=0.002$). AUROC was 68% for PEM and 96% for MRI ($p<0.001$). Among women undergoing biopsies, the positive predictive value (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 (2005) 4-site clinical study, Tafra et al 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.

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 since biopsy confirmation would be employed to resolve any false-positive results before changing overall cancer management approach.

PEM FOR A SUSPICIOUS BREAST LESION ON CONVENTIONAL BREAST CANCER EVALUATION
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 histologic review as criterion standard, including 3 studies described in detail next, were included. Pooled sensitivity and specificity were 85% (95% confidence interval [CI], 83% to 88%; I^2=74%) and 79% (95% CI, 74% to 83%; I^2=63%), respectively. Pooled PPVs and negative predictive values (NPVs) 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. 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. Median time from injection to imaging was 99 minutes; imaging took 10 minutes per image, and median slice thickness was 5.2 mm. 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, 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 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 US (when available) yielded sensitivity and specificity of 98% and 41%, respectively. (Specificity of PEM combined with conventional imaging was lower than PEM alone due to the 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. There were no false-negative lesions 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 ROC 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.

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 do not favor its use given that with alternative tests administer lower doses. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

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02/03/2011	Medical Policy Committee review
05/02/2011	Medical Policy Implementation Committee approval. New Policy.
02/02/2012	Medical Policy Committee review
02/15/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/07/2013	Medical Policy Committee review
02/20/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/05/2015	Medical Policy Committee review
02/18/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
02/04/2016	Medical Policy Committee review
02/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

Positron Emission Mammography (PEM)

Policy # 00285
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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	78811, 78999
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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

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

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