Scintimammography and Gamma Imaging of the Breast and Axilla

Policy # 00438
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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.

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

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

Based on review of available data, the Company may consider use of gamma detection following radiopharmaceutical administration for localization of sentinel lymph nodes in patients with breast cancer to be eligible for coverage.

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 scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) in all applications, including but not limited to their use as an adjunct to mammography or in staging the axillary lymph nodes to be investigational.

Background/Overview
Scintimammography, BSGI, and MBI all refer to the use of radiotracers with nuclear medicine imaging as a diagnostic tool for abnormalities of the breast. These tests are distinguished by use of differing gamma camera technology which may improve diagnostic performance for detecting small lesions with BSGI or MBI. BSGI uses single-head breast-specific gamma camera and a compression device; whereas, MBI uses dual-head breast-specific gamma cameras that also produce breast compression. Preoperative lymphoscintigraphy and/or intraoperative hand-held gamma detection of sentinel lymph nodes is a method of identifying sentinel lymph nodes for biopsy after radiotracer injection. Surgical removal of 1 or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer.

Mammography is the main screening modality for breast cancer, despite its limitations in terms of less than ideal sensitivity and specificity. Limitations of mammography are a particular issue for women at high risk of breast cancer, for whom cancer risk exceeds the inconvenience of more frequent screening, starting at a younger age, with more frequent false-positive results. Furthermore, the sensitivity of mammography is lower in women with radiographically dense breasts, which is more common among younger women. The clinical utility of adjunctive screening tests is primarily in the evaluation of women with inconclusive results on mammography. A biopsy is generally performed on a breast lesion if imaging cannot rule out malignancy with certainty. Therefore, adjunctive tests will be most useful in women with inconclusive mammograms if
they have a high negative predictive value (NPV), and can preclude the need for biopsy. Additional imaging for asymptomatic women who have dense breasts and negative mammograms has been suggested, but the best approach is subject to debate (TEC Special Report).

Scintimammography is a diagnostic modality using radiopharmaceuticals to detect breast tumors. After intravenous injection of a radiopharmaceutical, the breast is evaluated using planar imaging. Scintimammography is performed with the patient lying prone and the camera positioned laterally, which increases the distance between the breast and the camera. Special camera positioning to include the axilla may be included when the area of interest is evaluation for axillary metastases. Scintimammography using conventional imaging modalities has relatively poor sensitivity in detecting smaller lesions (eg, <15 mm), because of the relatively poor resolution of conventional gamma cameras in imaging the breast.

Breast-specific gamma imaging and MBI were developed to address this issue. Breast-specific gamma cameras acquire images while the patient is seated in a position similar to that in mammography and the breast is lightly compressed. Detector heads are immediately next to the breast, increasing resolution, and images can be compared with mammographic images. BSGI and MBI differ primarily in the number and type of detectors used (eg, multicrystal arrays of cesium iodide or sodium iodide, or nonscintillating, semiconductor materials, such as cadmium zinc telluride). In some configurations, a detector is placed on each side of the breast and used to lightly compress it. The maximum distance between the detector and the breast is therefore from the surface to the midpoint of the breast. Much research on BSGI and MBI has been conducted at the Mayo Clinic. The radiotracer typically used is technetium Tc-99m sestamibi. MBI imaging takes approximately 40 minutes.

Preoperative lymphoscintigraphy and/or intraoperative hand-held gamma detection of sentinel lymph nodes is a method of identifying sentinel lymph nodes for biopsy after radiotracer injection. Surgical removal of 1 or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer. Several trials have compared outcomes following sentinel lymph node biopsy versus axillary lymph node dissection for managing patients with breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-32 examined whether sentinel lymph node dissection (SLND) provides similar survival and regional control as full axillary lymph node dissection in the surgical staging and management of patients with clinically invasive breast cancer. This multicenter randomized controlled trial included 5611 women and observed statistically similar results for overall survival, disease-free survival, and regional control based on 8-year Kaplan-Meier estimates. Moreover, additional 3-year follow-up of morbidity after surgical node dissection revealed lower morbidity in the SLND group, including lower rates of arm swelling, numbness, tingling, and fewer early shoulder abduction deficits.4 A recent systematic review and meta-analysis by Ram et al (2014) reported no significant difference in overall survival (hazard ratio [HR], 0.94; 95% confidence interval [CI], 0.79 to1.19), no significant difference in disease-free survival (HR=0.83; 95% CI, 0.60 to 1.14), and similar rates of locoregional recurrence. However, axillary node dissection was associated with significantly greater surgical morbidity (eg, wound infection, arm swelling, motor neuropathy, numbness) than sentinel node biopsy.
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Radiopharmaceuticals
Scintimammography, BSGI, and MBI
The primary radiopharmaceutical used with BSGI or MBI is technetium 99m (Tc 99m) sestamibi. The product label states that Tc 99m sestamibi is “indicated for planar imaging as a second-line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass. Technetium Tc-99m sestamibi is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and it is not an alternative to biopsy.”

Technetium TC-99m tetrofosmin (Myoview™‡), a gamma-emitter used in some BSGI studies, is approved by the Food and Drug Administration only for cardiac imaging.

Pre- or Intraoperative Lymphoscintigraphy and/or Hand-Held Gamma Detection of Sentinel Lymph Nodes
The primary radiopharmaceuticals used for lymphoscintigraphy include Tc 99m pertechnetate-labeled colloids and Tc 99m tilmanocept (Lymphoseek). Whereas, Tc 99m sulfur colloid may be frequently used for intraoperative injection and detection of sentinel lymph nodes using hand-held gamma detection probe.

Radiation Exposure
The radiation dose associated with BSGI is substantial for diagnostic breast imaging modalities. According to Appropriateness Criteria from the ACR, the radiation dose from BSGI is 10 to 30 mSv, which is 15 to 30 times higher than the dose from a digital mammogram. According to ACR Appropriateness Criteria, at these levels BSGI is not indicated for breast cancer screening.

According to another study by Hruska and O’Connor (who report receiving royalties from licensed technologies by an agreement with Mayo Clinic and Gamma Medica), the effective dose from a lower “off-label” administered dose of 240-300 MBq (6.5-8 mCi) of Tc 99m sestamibi that is made feasible with newer dual-head MBI systems, is 2.0-2.5 mSv. For comparison, the effective dose (i.e., mean glandular dose) of digital mammography is estimated to be about 0.5 mSv. However, it is important to note that the dose for MBI is given to the entire body. The authors compared this dose with the estimated annual background radiation, which varies worldwide between 2.5 – 10 mSv and asserted that the effective dose from MBI “is considered safe for use in routine screening.”

Another article published online in August 2010 calculated mean glandular doses, and from those, lifetime attributable risks (LAR) of cancer, due to film mammography, digital mammography, BSGI, and positron emission mammography (PEM). The author, who is a consultant to GE Healthcare and a member of the medical advisory boards of Koning (manufacturer of dedicated breast computed tomography [CT]) and Bracco (MR contrast agents), used group risk estimates from the Biological Effects of Ionizing Radiation (BEIR) VII report to assess the risk of radiation-induced cancer and mortality from breast imaging studies. For a patient with average-sized breasts (compressed thickness during mammography of 5.3 cm per breast), estimated LARs of cancer at age 40 were:

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

Corresponding LARs of cancer mortality at age 40 were:
- 1.3 per 100,000 for digital mammography (breast cancer only),
- 1.7 per 100,000 for screen film mammography (breast cancer only),
- 26-39 per 100,000 for BSGI, and
- 31 for 100,000 for PEM.

A major difference in the impact of radiation between mammography, on the one hand, and BSGI or PEM, on the other, is that for mammography, the substantial radiation dose is limited to the breast. With BSGI and PEM, all organs are irradiated, increasing the risks associated with BSGI and PEM.

Notes: The term “molecular breast imaging” is used in different ways, sometimes for any type of breast imaging involving molecular imaging, including PEM, and sometimes limited to imaging with a type of breast-specific gamma camera, as used in this policy.

Use of single positron emission computed tomography (SPECT) and positron emission tomography (PET) of the breast are not covered in this policy.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

Several scintillation (gamma) cameras have general 510(k) marketing clearance from FDA, which states that they are cleared for “measuring and imaging the distribution of radionuclides in the human body by means of photon detection.” Two examples of gamma cameras used in BSGI or MBI (FDA Product Code IYX) are Dilon 6800®‡ (Dilon Technologies, Newport News, VA) and single-head configurations of Discovery NM750b (GE Healthcare, Milwaukee, WI). Dual-head cameras used in molecular breast imaging include LumaGEM™‡ (Gamma Medical, Salem, NH) (FDA product code IYX) and Discovery NM750b (GE Healthcare, Milwaukee, WI).

Technetium 99m (Tc-99m) sestamibi (marketed by Draxis Specialty Pharmaceuticals, Cardinal Health 14, Mallinckrodt, and Pharmalucence) has been approved by FDA with the following labelling: “Breast Imaging: Technetium TC 99M Sestamibi is indicated for planar imaging as a second line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass. Technetium TC 99M Sestamibi is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and it is not an alternative to biopsy.”

In March 2013, Tc 99m tilmanocept (Lymphoseek; Navidea Biopharmaceuticals) was first approved by FDA for use in breast cancer and melanoma as a radioactive diagnostic imaging agent to help localize lymph nodes.

Technetium-99m-sulfur colloid has approved by FDA through the new drug application (GE Healthcare, NDA 017456; Mallinckrodt, NDA 017724) process although these products appear to no longer be marketed. In addition, in 2011, Technetium Tc 99m Sulfur Colloid Kit (Pharmalucence) was approved by...
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FDA through the NDA process (NDA 017858) for use as an injection to localize lymph nodes in breast cancer patients.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
Scintimammography, Breast-Specific Gamma Imaging, and Molecular Breast Imaging
Dense Breasts or High Risk for Breast Cancer
Several studies have assessed breast-specific gamma imaging (using either BSGI or MBI) in women at high risk for breast cancer. Rhodes et al (2011) prospectively compared MBI (with dual-head cadmium zinc telluride detectors), mammography, and the combination of the 2 modalities in 936 asymptomatic women with heterogeneously or extremely dense breasts on prior mammogram, as well as additional risk factors (BRCA mutations, a personal history of breast cancer). Risk in these different populations varies substantially. Eleven (1.2%) of 936 women were diagnosed with cancer. Overall sensitivity was 82% (95% confidence interval [CI], 52% to 95%) for MBI, 27% (95% CI, 10% to 57%) for mammography, and 91% (95% CI, 62% to 98%) for both combined. Specificity was 93% (95% CI, 91% to 94%) for MBI, 91% (95% CI, 89% to 93%) for mammography, and 85% (95% CI, 83% to 87%) for both (sensitivity and specificity for MBI vs mammography, both p=0.07). The number of breast cancers diagnosed per number of biopsies performed was 28% for MBI and 18% for mammography.

In 2015, Rhodes et al reported a similar prospective study that evaluated MBI using a lower dose of technetium Tc 99m (Tc 99m) sestamibi (dispensed activity, 300 MBq [≈2.4 mSv] vs 740 MBq in conventional doses). Like the earlier study by this research group, study participants were asymptomatic and had heterogeneously or extremely dense breasts. More than half (57%) had an additional risk factor for breast cancer, conferring varying degrees of risk (eg, 10% had a personal history of breast cancer) and 22% (without personal history of breast cancer) had elevated Gail model risk. Of 1651 eligible women, 1585 (96%) underwent both mammography and MBI. Images were interpreted by radiologists blinded to results of the other test using a standardized lexicon, and reference standards included follow-up of both positive and negative test results for 11 months minimum. Twenty-one (1.3%) of 1583 women were diagnosed with cancer. For detection of all cancers (invasive cancers plus ductal carcinoma in situ [DCIS]), sensitivity was 24% (95% CI, 11% to 45%) for mammography versus 91% (95% CI, 71% to 97%) for mammography plus MBI (p<0.001); specificity was 89% (95% CI, 88% to 91%) versus 83% (95% CI, 81% to 85%; p<0.001); positive predictive value (PPV) was 3% (95% CI, 1% to 7%) versus 7% (95% CI, 4% to 10%; p=0.021); and negative predictive value (NPV) was 99% (95% CI, 98% to 99%) versus 100% (95% CI, 99% to 100%; p<0.001), all respectively. The addition of MBI increased the recall rate from 11% with mammography alone to 18% (p<0.001), and the biopsy rate from 1% to 4% (p<0.001).

Several studies have evaluated the diagnostic accuracy of BSGI in patients with dense breasts or high risk for breast cancer who had normal mammographic findings. Brem et al (2005) prospectively evaluated 94 women with BSGI who considered at high risk of breast cancer despite normal mammographic findings. High risk was defined as a 5-year breast cancer risk of 1.66%, as determined by the Gail model. Of 94
women in the study, 35 (37%) had a prior history of some type of breast cancer or atypical hyperplasia. Sixteen (17%) women had abnormal BSGI findings. Follow-up ultrasounds in 11 of these identified a hypoechoic lesion that was biopsied. The 5 remaining patients had normal ultrasound results and were followed with repeat BSGI at 6 months, which was normal in all 5. Among the 11 women who underwent ultrasound-guided biopsy, 2 (12%) invasive cancers were identified. The sensitivity of BSGI was 100% (95% CI, 22% to 100%) and specificity was 85%. The study was limited by the small number of cancers detected.

Two retrospective studies were published in 2016. Shermis et al reported on women with dense breasts and negative mammograms. The study sample was taken from a population of asymptomatic women who presented for routine breast cancer screening with mammography; a subset of these women were referred for supplemental screening. Women with Breast Imaging Reporting and Data System (BI-RADS) category 1 or 2 findings on mammography (ie negative or benign) who had a BI-RADS density category C or D (ie heterogeneously or extremely dense) and whose lifetime risk was less than 20% according to the Gail model were recommended for supplemental MBI screening. (Women with similar characteristics but a 20% or greater lifetime risk of breast cancer were recommended for magnetic resonance imaging [MRI] screening.) The MBI protocol was similar to that used in the Rhodes clinic studies (ie, use of 300 MBq of Tc 99m sestamibi). Of 1696 women who received supplemental MBI, 143 (8.4%) had a positive finding and 13 (9%) of these 143 women were confirmed histopathologically as malignancies. Two of the malignancies were DCIS and 11 were malignancies. Thus, the incremental cancer detection rate with MBI was 0.77% (13/1696) and an invasive cancer rate of 0.65% (11/1696). The recall rate was 8.4% (143/1696). As the authors noted, follow-up was not conducted on all 1696 women so the sensitivity and specificity of MBI in this study population could not be determined.

Also in 2016, Brem et al retrospectively reviewed findings of BSGI in 849 women at increased risk of breast cancer (eg, BRCA1, BRCA2, family history of breast cancer) whose mammogram findings were classified as negative, benign, or probably benign (BI-RADS categories 1, 2, or 3). BSGI examinations were performed with a single-head high-resolution breast-specific gamma camera, initially at a mean of 781 MBq Tc 99m sestamibi (n=653) but the protocol was then modified to a mean of 296 MBq (n=196). A total of 212 (25%) of 849 women had a positive BSGI examination (recall rate). Fourteen (6.6%) of the 212 women who tested positive were found to have breast cancer. Eight of the 14 cancers were DCIS. The incremental cancer detection rate with BSGI was 1.6% (14/849) and the invasive cancer rate was 0.7% (6/849).

Although the use of BSGI (or MBI) has been proposed for women at high risk of breast cancer, there is controversy and speculation over whether some women (eg, those with BRCA mutations) have a heightened radiosensitivity. If women with BRCA mutations are more radiosensitive than the general population, studies may underestimate the risks of breast imaging with ionizing radiation (ie, mammography, BSGI, molecular breast imaging (MBI), positron emission mammography, single-photon emission computed tomography/computed tomography, breast-specific computed tomography, and tomosynthesis) in these women. In contrast, ultrasonography and MRI do not use radiation. More research will be needed to resolve this issue. Also, the risk associated with radiation exposure will be greater for women at high risk of breast cancer, whether or not they are more radiosensitive, because they start screening at a younger age when the risks associated with radiation exposure are greater.
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Section Summary: Dense Breasts or High Risk for Breast Cancer
There are 3 prospective studies comparing the incremental difference in diagnostic accuracy when BSGI or MBI is added to mammography in women at increased risk, and both the MBI studies were by the same research group. Sensitivity was higher with combined BSGI (or MBI) and mammography, but specificity was lower. Studies of women at increased risk of breast cancer and negative mammograms found that a small number of additional cancers were detected, but the recall rate was relatively high. Studies tended to include women at different risk levels (eg, women with dense breasts and those with BRCA1). Moreover, any potential benefits need to be weighed against potential risks of additional radiation exposure and risks to breast biopsy for false-negative findings. Even in studies that used a reduced dose of Tc 99m sestamibi, the effective dose (2.4 mSv) exceeded that of digital mammography (≈0.5 mSv) by a factor of 4.8. In addition, a large, high-quality, head-to-head comparison of BSGI (or MBI) and MRI would be needed, especially for women at high risk of breast cancer, because MRI, alternated with mammography, is currently the recommended screening technique.

Indeterminate or Suspicious Breast Lesions
Several studies have addressed BSGI in women who have indeterminate or suspicious lesions. Spanu et al (2012) assessed the clinical impact of BSGI (using Tc 99m Tetrofosmin) in a prospective study of 467 women who had suspicious lesions on physical examination, MRI, ultrasound, or mammogram. Histopathology reports were obtained in all cases. BSGI results were true positive in 408 of 420 breast cancer patients (sensitivity, 97%), including the detection of multifocal, multicentric disease and bilateral disease, and were false negative in 12 breast cancer patients. BSGI results were true negative in 40 of 47 patients with benign lesions (specificity, 85%). The authors calculated that BSGI provided additional value compared with mammography in 141 (30%) of 467 patients, 108 with breast cancer and 33 with benign lesions.

In a 2008 study by Hruska et al, 150 patients with BI-RADS classification 4 or 5 lesions smaller than 2 cm identified on mammography or ultrasound who were scheduled for biopsy underwent MBI using a dual-head, breast-specific gamma camera. Results from 3 blinded readers were averaged. In 88 patients, 128 cancer tumors were found. The per-lesion sensitivity with the dual-head camera was 90% (115/128) for all lesions and 82% (50/61) for lesions 1 cm or smaller. Overall, MBI specificity (by patient) was 69%. The proportion of patients with cancer in this study was higher than might be expected in a screening population with suspicious lesions on mammography. In selecting patients, preference was given to those who had a high suspicion of cancer or were likely to have multifocal or multicentric disease.

Spanu et al (2008) evaluated 145 consecutive patients scheduled for breast biopsy with MBI (using Tc 99m Tetrofosmin). With an 86% prevalence of disease, sensitivity of MBI was 98% per patient (100% for tumors >10 mm, 91% for tumors ≤10 mm). Per-lesion specificity was 86%. Four cancers were missed, 3 of which were detected by mammography. The authors suggested using MBI for surgical planning or to avoid biopsy, but the NPV (83%) was not high enough to forgo biopsy.

Brem et al (2007) compared BSGI and MRI in 23 women with 33 indeterminate lesions. Eight patients had 9 pathologically confirmed cancers. BSGI demonstrated a significantly greater specificity (71%; 95% CI, 49% to 87%) than MRI (25%; 95% CI, 11% to 47%; p<0.05) and comparable sensitivity (BSGI, 89% [95% CI,
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51% to 99% vs MRI, 100% [95% CI, 63% to 100%]), PPV (BSGI, 53% [95% CI, 27% to 78%] vs MRI, 33% [95% CI, 17% to 54%]), and NPV (BSGI, 94% [95% CI, 71% to 100%] vs MRI, 100% [95% CI, 52% to 100%]). The authors noted that the 100% sensitivity and 25% specificity of MRI would likely was due to the small number of cancers in the study.

In 2014, Tan et al assessed the diagnostic accuracy of dual-phase BSGI (at 10-15 minutes and at 90-120 minutes) in 76 women at a single institution in China who had suspicious breast masses. On pathologic review, 54 (59%) of 92 tumors were malignant and 38 (41%) were benign. Using receiver operating characteristic determined cut points for visual and semiquantitative interpretation, sensitivity and specificity were maximized when a combination of visual and early-phase semiquantitative interpretation was used (85% and 92%, respectively) compared with either analysis or delayed-phase semiquantitative analysis alone.

Meissnitzer et al (2015) in Austria evaluated BSGI in the diagnostic workup of 67 patients with 92 breast lesions identified on mammography and/or ultrasonography. Biopsy results were obtained as the reference standard in all patients, and 67 (73%) of 92 lesions were malignant. BSGI images were interpreted visually and semiquantitatively. Overall BSGI sensitivity and specificity were 90% and 56%, respectively, compared with ultrasound sensitivity and specificity of 99% and 20%, respectively. For lesions smaller than 1 cm, sensitivity of BSGI was 60%.

In 2016, Cho et al retrospectively reviewed breast lesions in 162 women diagnosed with BI-RADS category 4 lesions (suspicious) on mammography or ultrasonography. Patients had subsequently undergone BSGI with 925 to 1110 MBq of Tc 99m sestamibi. Using biopsy-confirmed pathologic evaluation as the criterion standard, 66 (40.7%) of 162 lesions were found to be malignant. The sensitivity and specificity of BSGI were 90.9% (95% CI, 81.3% to 96.6%) and 78.1% (95% CI, 68.5% to 85.9%), respectively. The PPV was 74.1% (95% CI, 63.1% to 83.2%) and the NPV was 92.6% (95% CI, 84.6% to 97.2%). For lesions less than 1 cm, the sensitivity of BSGI was 88.0% (95% CI, 86.6% to 97.5%) and the specificity was 86.8% (95% CI, 71.9% to 95.6%). For lesions greater than 1 cm, the sensitivity was higher (92.7%; 95% CI, 80.1% to 98.5%) and the specificity was lower (61.5%; 95% CI, 44.6% to 76.6%).

Section Summary: Indeterminate or Suspicious Breast Lesions

A number of studies have evaluated the diagnostic accuracy of BSGI (or MBI) of suspicious lesions. Compared with biopsy, the NPV in studies that reported this outcome varied from 83% to 94%. The value of BSGI in evaluating indeterminate or suspicious lesions must be compared with other modalities that would be used (eg, spot views ultrasound, MRI) for diagnostic mammography. Given the relative ease and diagnostic accuracy of the criterion standard (biopsy), coupled with the adverse consequences of missing a breast cancer, the NPV of BSGI would have to be extremely high to alter treatment decisions. Because NPV is partially determined by disease prevalence, NPV will be lower in a population of patients with mammographic abnormalities highly suggestive of breast cancer than in a population of patients with mammographic abnormalities not suggestive of breast cancer. Therefore, any clinical utility of BSGI as an adjunct to mammography would vary by type of mammographic abnormalities included in the studies.
Detection of Residual Tumor After Neoadjuvant Therapy

A 2016 systematic review and meta-analysis by Guo et al identified 14 studies investigating the performance of Tc 99m BSGI for evaluating the response to neoadjuvant therapy in patients with breast cancer. In all studies, histopathologic results were obtained after surgery and used as the criterion standard. Study sizes ranged from 14 to 122 patients (total N=503 patients). Most studies had fewer than 30 patients. Thirteen studies were prospective and 1 retrospective. Only 3 studies conducted BSGI both before and after treatment. The sensitivity of BSGI for identifying residual disease ranged from 33% to 100%, with a pooled sensitivity of 86% (95% CI, 78% to 92%). The specificity ranged from 17% to 95%, and the pooled specificity was 69% (95% CI, 64% to 74%).

The largest study, published by Lee et al in 2014, was retrospective and single-center. It evaluated BSGI detection of residual tumor after neoadjuvant chemotherapy (primarily anthracycline and taxane-based) in 122 women who had pathologically confirmed invasive breast cancer. All patients underwent BSGI and dynamic contrast-enhanced breast MRI after completing neoadjuvant therapy. Surgeons consulted BSGI and MRI for surgical planning (ie, either breast-conserving therapy [64%]) or mastectomy [36%]). Of 122 patients, 104 (85%) had residual disease by pathologic review. BSGI sensitivity was 74%, specificity was 72%, NPV was 33%, and PPV was 94%. Sensitivity of BSGI varied with cellularity and size of residual tumor (greater sensitivity with greater cellularity and greater size).

No studies were identified that compared imaging methods (eg, BSGI vs MRI or fluorodeoxyglucose fluorine 18 positron emission tomography) for detection of residual tumor after neoadjuvant therapy. In addition, no studies were identified on the clinical utility of BSGI, ie, changes in patient management strategies such as the extent of surgery or in health outcomes such as disease-specific survival.

Section Summary: Detection of Residual Tumor After Neoadjuvant Therapy

A meta-analysis of studies evaluating BSGI for detecting residual tumor after neoadjuvant therapy found a pooled sensitivity of 86% and a pooled specificity of 69%, compared to histopathologic analysis. No studies were identified that compared the diagnostic accuracy of BSGI with other imaging approaches or that investigated the impact of BSGI on patient management decisions or health outcomes.
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**Section Summary: Detection of Residual Tumor After Neoadjuvant Therapy**
A meta-analysis of studies evaluating BSGI for detecting residual tumor after neoadjuvant therapy found a pooled sensitivity of 86% and a pooled specificity of 69%, compared to histopathologic analysis. No studies were identified that compared the diagnostic accuracy of BSGI with other imaging approaches or that investigated the impact of BSGI on patient management decisions or health outcomes.

**Surgical Planning for Breast-Conserving Therapy**
Edwards et al (2013) retrospectively assessed changes in surgical management of 218 women who had breast cancer and were eligible for breast-conserving therapy. All patients had undergone preoperative BSGI or MRI. Twelve percent of patients who had BSGI and 29% of those who had MRI changed to mastectomy. On pathologic review, no patient who underwent mastectomy was eligible for breast-conserving therapy. Of patients who received breast-conserving therapy, 15% of those who had BSGI and 19% of those who had MRI required a single reexcision because of positive surgical margins, and 14% and 6%, respectively, required mastectomy. Based on this retrospective study, the clinical utility of BSGI for guiding surgical decision making in breast cancer patients appears limited.

**Section Summary: Surgical Planning for Breast-Conserving Therapy**
One retrospective study is insufficient to determine the clinical utility of BSGI for guiding surgical decision making in breast cancer patients. In this study, it appeared as if MRI identified more patients than BSGI who were not appropriate candidates for breast-conserving therapy. Prospective comparative studies are needed.

**Detection of Axillary Metastases**
Regarding the use of scintimammography to detect axillary metastases, a review of studies published between 1994 and 1998 showed a sensitivity of 77% and specificity of 89%. More recent studies using different radiopharmaceuticals have shown sensitivities in the high 80% to 90% range. A 2011 meta-analysis reviewed 45 studies of scintimammography and also reported sensitivities and specificities in this range, with summary estimates for sensitivity of 83% (95% CI, 82% to 84%) and for specificity of 85% (95% CI, 83% to 86%). The test still is not accurate enough to replace surgical nodal dissection. No studies have examined patient outcomes comparing the strategy of using scintimammography to aid in decision making regarding nodal dissection versus going directly to nodal dissection.
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Section Summary: Detection of Axillary Metastases

Current evidence on BSGI for detection of axillary metastases comprises small studies and systematic reviews of these studies. A meta-analysis of 45 small studies found that pooled sensitivity was 93% and pooled specificity was 85%; the diagnostic accuracy of BSGI as reported in the available literature is not high enough for this technology to replace the current standard practice (surgical nodal dissection). Moreover, clinical utility studies of scintimammography to guide decision making in this setting are lacking.

Localization of Sentinel Lymph Nodes Using Radiopharmaceutical and Gamma Detection

Pesek et al (2012) published a meta-analysis based on search between 1993 and 2011; 183 articles met inclusion criteria (total N=9306 patients). This analysis examined the results for the false-negative rate (FNR) of sentinel node biopsy in patients with breast cancer separately by use of localization technique: radioactive tracer alone, dye alone, or combination of radioactive tracer and dye. The FNR was highest for dye-only group at 8.6% (95% CI, 6.7% to 10.8%) while the tracer-only group had FNR of 7.4% (95% CI, 5.6% to 9.3%), and the combination of dye-and-tracer had the lowest FNR at 5.9% (95% CI, 4.8% to 7.1%). The Q-statistic for heterogeneity indicated that the 3 groups were not all equal (p=0.050). Subsequent pairwise comparisons revealed a difference between the dye-only and the dye-and-tracer categories (p=0.018), but no significant difference was seen between tracer-only and dye-only (p=0.370) or between tracer-only and dye-and-tracer (p=0.178).

A randomized study by van der Vorst et al (2012) compared Tc 99m radiotracer combined with near-infrared fluorescence imaging using indocyanine green with or without use of patent blue dye for localization of sentinel lymph nodes. Twenty-four consecutive breast cancer patients who were all undergoing sentinel lymph node biopsy were studied. Of the 23 cases where sentinel lymph node mapping was successful, the sentinel lymph nodes were both radioactive and fluorescent in 100% of cases, whereas only 84% of the sentinel lymph nodes showed blue dye staining. In addition, for 25% of cases, the gamma probe was needed to identify and locate the sentinel nodes during the first 15 minutes of localization.

Johnson et al (2011) reported a single institution study assessing 699 patients with operable breast cancer for sentinel lymph node biopsy. Using intraoperative Tc 99m-labelled radiopharmaceutical tracer subareolar injection, the sentinel node was localized in 98.6% of cases.

Martin et al (2000) reported a prospective multi-institutional study examining 758 patients who were clinical stage T1-2, N0, M0 invasive breast cancer and who had injection of both radioactive colloid and isosulfan blue dye before axillary sentinel lymph node biopsy. Localization of sentinel nodes was successful in 89% of cases and 33% of histologically positive sentinel lymph nodes showed no blue dye staining.

Some studies have examined whether preoperative lymphoscintigraphy improves sentinel node localization and detection in clinically node-negative patients and have found little or no incremental value for lymphoscintigraphy imaging of the axilla. Note that lymphoscintigraphy uses planar or tomographic imaging that differs from use of hand-held gamma detection probe of radioactive nodes during surgery.
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Section Summary: Localization of Sentinel Lymph Nodes Using Radiopharmaceutical and Gamma Detection

For individuals who have breast cancer undergoing sentinel lymph node biopsy for detection of axillary metastases who receive radiopharmaceutical and gamma detection for localization of sentinel lymph nodes, the evidence includes 3 studies and a meta-analysis. These studies provide consistent evidence that diagnostic performance using radiopharmaceutical and gamma detection for localization of sentinel lymph nodes yield high success rates in identifying sentinel lymph nodes and trend toward better detection rates using radiopharmaceutical compared to alternative methods using only blue dye. Clinical utility is demonstrated for this indication when the high diagnostic yield of SLN using radiopharmaceutical and gamma detection is considered together with the evidence that sentinel lymph node biopsy provides similar long-term outcomes as full axillary lymph node dissection for control of breast cancer and offers more favorable early results with reduced arm swelling and postsurgical morbidity. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might impact this policy 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>
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<td>Tc99m Sestamibi Molecular Breast Imaging</td>
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<tr>
<td>NCT02324387</td>
<td>Breast-Specific Gamma Imaging and Locally Advanced Breast Cancer Undergoing Neoadjuvant Chemotherapy (BSGILAB)</td>
<td>200</td>
<td>Oct 2020</td>
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</table>

NCT: national clinical trial.

Summary

Scintimammography, Breast-Specific Gamma Imaging, and Molecular Breast Imaging

For individuals who have dense breasts or high risk for breast cancer who receive scintimammography, BSGI or MBI as adjunct to mammography, the evidence includes diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. There are 3 prospective studies comparing the incremental difference in diagnostic accuracy when BSGI (or MBI) is added to mammography in women at increased risk. Sensitivity was higher with combined BSGI (or MBI) and mammography, but specificity was lower. Studies of women at increased risk of breast cancer and negative mammograms found that a small number of additional cancers were detected but the recall rate was relatively high. Studies tended to include women at different risk levels (eg, women with dense breasts and those with BRCA1). Moreover, any potential benefits need to be weighed against potential risks of additional radiation exposure. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have indeterminate or suspicious breast lesions who receive scintimammography and BSGI, the evidence includes diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. In the available studies, compared with biopsy, the NPV of BSGI (or MBI) varied from 83% to 94%. Given the relative ease and
diagnostic accuracy of the criterion standard of biopsy, coupled with the adverse consequences of missing a breast cancer, the NPV of BSGI (or MBI) would have to be extremely high to alter treatment decisions. The evidence to date does not demonstrate this level of NPV. Moreover, the value of BSGI in evaluating indeterminate or suspicious lesions must be compared with other modalities that would be used, such as spot views for diagnostic mammography. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have breast cancer undergoing detection of residual tumor after neoadjuvant therapy who receive scintimammography and BSGI, the evidence includes diagnostic accuracy studies and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. The meta-analysis of studies evaluating the accuracy of BSGI for detecting residual tumor after neoadjuvant therapy found a pooled sensitivity of 86% and a pooled specificity of 69%, compared to histopathologic analysis. No studies were identified that compared the diagnostic accuracy of BSGI with other imaging approaches or that investigated the clinical utility of this potential application of BSGI. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have breast cancer undergoing surgical planning for breast-conserving therapy who receive scintimammography and BSGI, the evidence includes 1 retrospective observational study. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. In the retrospective study, it appeared that magnetic resonance imaging identified more patients than BSGI who were not appropriate candidates for breast-conserving therapy. Prospective comparative studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have breast cancer undergoing detection of axillary metastases who receive scintimammography and BSGI, the evidence includes diagnostic accuracy studies and systematic reviews of diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. A meta-analysis of the available diagnostic accuracy studies found that the sensitivity and specificity of BSGI is not high enough for this technology to replace the current standard practice, surgical nodal dissection. The evidence is insufficient to determine the effects of the technology on health outcomes.

Localization of Sentinel Lymph Nodes Using Radiopharmaceutical and Gamma Detection

For individuals who have breast cancer undergoing sentinel lymph node biopsy for detection of axillary metastases who receive radiopharmaceutical and gamma detection for localization of sentinel lymph nodes, the evidence includes 3 studies and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. A meta-analysis and 3 additional studies have provided evidence that diagnostic performance using radiopharmaceutical and gamma detection for localization of sentinel lymph nodes yield high success rates in identifying sentinel lymph nodes and trend toward better detection rates using radiopharmaceutical compared to alternative methods (eg, using only blue dye). The evidence has indicated that sentinel lymph node biopsy provides similar long-term outcomes as full axillary lymph node dissection for control of breast cancer and offers
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more favorable early results with reduced arm swelling and better quality of life. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

References
18. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Breast-specific gamma imaging (BSGI), molecular breast imaging (MBI), or scintimammography with breast-specific gamma camera. TEC Assessments 2013; Volume 28, Tab 2.
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09/04/2014 Medical Policy Committee review
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015 Medical Policy Committee review

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11/03/2016  Medical Policy Committee review
11/16/2016  Medical Policy Implementation Committee approval. New policy statement added for gamma
detection following radiopharmaceutical administration for localization of sentinel lymph nodes.
01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes and HCPCS code update

Next Scheduled Review Date: 11/2017

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are
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Applicable FARS/DFARS apply.

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

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<th>Code Type</th>
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<td>A4641, A4642, A9500, A9502, A9568, A9572, S8080 New codes 1/1/17: A9597, A9598</td>
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<td>ICD-10 Diagnosis</td>
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*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. 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
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of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown
by reliable evidence, including:
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      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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**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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

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

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