**Policy Statement**

Use of breast-specific gamma detection following radiopharmaceutical administration for localization of sentinel lymph nodes in patients with breast cancer may be considered **medically necessary**.

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

**Policy Guidelines**

The most commonly used radiopharmaceutical in breast-specific gamma imaging or molecular breast imaging is technetium 99m (Tc 99m) sestamibi. There is a specific HCPCS code for this radiopharmaceutical:

- **A9500**: Technetium Tc-99m sestamibi, diagnostic, per study dose, up to 40 millicuries

The 2013 Breast Imaging Reporting and Data System (BI-RADS) breast assessment and breast tissue categories are summarized in Table PG1.

<table>
<thead>
<tr>
<th>Grading Schema</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment categories</td>
<td>Incomplete</td>
</tr>
<tr>
<td>1</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>Benign</td>
</tr>
<tr>
<td>3</td>
<td>Probably benign</td>
</tr>
<tr>
<td>4</td>
<td>Suspicious</td>
</tr>
<tr>
<td>5</td>
<td>Highly suggestive of malignancy</td>
</tr>
<tr>
<td>6</td>
<td>Known biopsy-proven malignancy</td>
</tr>
</tbody>
</table>

**Breast tissue categories**

- a  Breasts are almost entirely fatty
- b  Scattered areas of fibroglandular density
- c  Heterogeneously dense
- d  Extremely dense

BI-RADS: Breast Imaging Reporting and Data System.

The most commonly used radiopharmaceuticals for sentinel lymph node detection using either lymphoscintigraphy or hand-held gamma detection include Tc 99m–labeled colloids (e.g., sulfur colloid).

The HCPCS code for this particular radiopharmaceutical is:

- **A9541**: Technetium Tc-99m sulfur colloid, diagnostic, per study dose, up to 20 millicuries

Among the other possible radiopharmaceuticals is Lymphoseek®, which is reported with the following HCPCS code:

- **A9520**: Technetium tc-99m, tilmanocept, diagnostic, up to 0.5 millicuries
The following HCPCS code is specific to scintimammography:

- **S8080**: Scintimammography (radioimmunoscintigraphy of the breast), unilateral, including supply of radiopharmaceutical

### Description

Scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) use radiotracers with nuclear medicine imaging as a diagnostic tool for abnormalities of the breast. These tests are distinguished by the use of differing gamma camera technology, which may improve diagnostic performance for detecting small lesions. BSGI uses a 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 one or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer.

### Related Policies

- N/A

### 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

Several scintillation (gamma) cameras have been cleared for marketing by the FDA through the 510(k) process for “measuring and imaging the distribution of radionuclides in the human body by means of photon detection.” Examples of gamma cameras used in BSGI are the Dilon 6800® (Dilon Technologies) and single-head configurations of Discovery NM750b (GE Healthcare). Dual-head cameras used in MBI include LumaGEM™ (Gamma Medical) (FDA product code IYX) and Discovery NM750b (GE Healthcare).

Tc-99m sestamibi (marketed by Draxis Specialty Pharmaceuticals, Cardinal Health 14, Mallinckrodt, and Pharmaluce) has been approved by the FDA with the following labeling: “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 2013, Tc 99m tilmanocept (Lymphoseek; Navidea Biopharmaceuticals) was approved by the FDA for use in breast cancer and melanoma as a radioactive diagnostic imaging agent to help localize lymph nodes. Technetium-99m-sulfur colloid was approved by the FDA through the new drug application (NDA; GE Healthcare, NDA 017456; Mallinckrodt, NDA 017724) process although these products appear to be marketed no longer. In addition, in 2011, Technetium Tc 99m Sulfur Colloid Kit (Pharmalucence) was approved by the FDA through the NDA process (NDA 017858) for use as an injection to localize lymph nodes in breast cancer patients.

In 2018, the FDA granted approval to Northstar Medical Radioisotopes for its RadioGenix™ System, which produces molybdenum 99, the material used to generate Tc 99m. Previously, molybdenum 99 was only produced from enriched uranium in facilities outside of the United States.

**Rationale**

**Background**

**Mammography**

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 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 (see the TEC Special Report [2013]1).

**Scintimammography**

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 an evaluation for axillary metastases. Scintimammography using conventional imaging modalities has relatively poor sensitivity in detecting smaller lesions (e.g., <15 mm), because of the relatively poor resolution of conventional gamma cameras in imaging the breast.

**Breast-Specific Gamma Imaging**

BSGI and molecular breast imaging (MBI) were developed to address the poor resolution of conventional gamma cameras. 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 (e.g., 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 compress it lightly. The maximum distance between the detector and the breast is therefore from the surface to the midpoint of the breast. The radiotracer typically used is technetium 99m (Tc 99m) sestamibi, and MBI takes approximately 40 minutes.2

**Lymphoscintigraphy and Hand-Held Gamma Detection**
Preoperative lymphoscintigraphy and/or intraoperative hand-held gamma detection of sentinel lymph nodes is a method of identifying sentinel lymph nodes for a biopsy after radiotracer injection. Surgical removal of one 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 with axillary lymph node dissection for managing patients who have breast cancer. The National Surgical Adjuvant Breast and Bowel Project trial B-32 examined whether sentinel lymph node dissection 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. An additional three-year follow-up of morbidity after surgical node dissection revealed lower morbidity in the sentinel lymph node dissection group, including lower rates of arm swelling, numbness, tingling, and fewer early shoulder abduction deficits. A recent systematic review and meta-analysis by Ram et al (2014) reported no significant difference in overall survival (hazard ratio, 0.94; 95% confidence interval, 0.79 to 1.19), no significant difference in disease-free survival (hazard ratio, 0.83; 95% confidence interval, 0.60 to 1.14), and similar rates of locoregional recurrence. However, axillary node dissection was associated with significantly greater surgical morbidity (e.g., wound infection, arm swelling, motor neuropathy, numbness) than sentinel node biopsy.

**Radiopharmaceuticals**

**Scintimammography, BSGI, and MBI**
The primary radiopharmaceutical used with BSGI or MBI is 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 (FDA) only for cardiac imaging.

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

**Radiation Exposure**

**Scintimammography, BSGI, and MBI**
The radiation dose associated with BSGI is substantial for diagnostic breast imaging modalities. According to Appropriateness Criteria from the American College of Radiology, the radiation dose from BSGI is 10 to 30 mSv, which is 15 to 30 times higher than the dose from a digital to the American College of Radiology, at these levels, BSGI is not indicated for breast cancer screening.

According to a study by Hruska and O'Connor (2015; who reported 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 to 300 MBq (6.5-8 mCi) of Tc 99m sestamibi that is made feasible with newer dual-head MBI systems, is 2.0 to 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 mSv and 10 mSv, and asserted that the effective dose from MBI "is considered safe for use in routine screening."
Hendrick (2010) calculated mean glandular doses and lifetime attributable risks of cancer due to film mammography, digital mammography, BSGI, and positron emission mammography (PEM). The author, a consultant to GE Healthcare and a member of the medical advisory boards of Koning (manufacturer of dedicated breast computed tomography) and Bracco (magnetic resonance contrast agents), used group risk estimates from the Biological Effects of Ionizing Radiation 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 lifetime attributable risks of cancer at age 40 were:

- 5 per 100000 for digital mammography (breast cancer only),
- 7 per 100000 for screen-film mammography (breast cancer only),
- 55 to 82 per 100000 for BSGI (depending on the dose of Tc 99m sestamibi), and
- 75 per 100000 for PEM.

Corresponding lifetime attributable risks of cancer mortality at age 40 were:

- 1.3 per 100000 for digital mammography (breast cancer only),
- 1.7 per 100000 for screen-film mammography (breast cancer only),
- 26 to 39 per 100000 for BSGI, and
- 31 per 100000 for PEM.

A major difference in the impact of radiation between mammography and BSGI or PEM 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 radiation exposure.

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 it is used synonymously with the term breast-specific gamma camera, as used in this review.

Use of single-photon emission computed tomography and positron emission tomography of the breast are not addressed in this review.

**Literature Review**

This review has been informed by a TEC Assessment (2013). Lymphoscintigraphy and radioactive localization for sentinel lymph node biopsy were not discussed in that TEC Assessment. The scope of this evidence review was expanded to include lymphoscintigraphy and radioactive localization for sentinel lymph node biopsy (SLNB).

A few studies have reported on the change in patient management after imaging but there were insufficient data to determine whether these changes led to improvements in health outcomes. A subsequent TEC Special Report (2013) reviewed evidence for asymptomatic women undergoing breast cancer screening, including those with dense breasts or at high risk of breast cancer. Retrospective studies included women with a mix of indications. For all indications, evidence was insufficient.

**Tests for Diagnosis**

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.
Scintimammography, Breast-Specific Gamma Imaging, and Molecular Breast Imaging for Diagnosis

Clinical Context and Test Purpose
Scintimammography, BSGI, and MBI are used to confirm a diagnosis of breast cancer for women with dense breasts or are at high-risk for breast cancer and in those with indeterminate breast lesions. These tests are also used to in patients with breast cancer to detect residual tumor in patients who have undergone neoadjuvant therapy or patients planning for breast-conserving therapy.

The questions addressed in this evidence review:
- Does the use of scintimammography, BSGI, or MBI as an adjunct to mammography improve the net health outcome compared with mammography alone, ultrasonography, or magnetic resonance imaging (MRI) in women with dense breasts or those at high-risk for breast cancer?
- Does the use of scintimammography, BSGI, or MBI improve the net health outcome compared with mammography spot compression views, ultrasonography, or MRI in women with indeterminate or suspicious breast lesions?
- Does the use of scintimammography or BSGI improve net health outcome compared with MRI, fluorine 18 fluorodeoxyglucose positron emission tomography, or ultrasonography in women with breast cancer undergoing evaluation for residual tumor after neoadjuvant therapy?
- Does the use of scintimammography or BSGI improve the net health outcome compared with MRI in women with breast cancer undergoing evaluation for undetected disease in those planning for breast-conserving surgery?

Dense Breasts or High-Risk for Breast Cancer
The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is women with dense breasts or those at high-risk for breast cancer, as part of routine screening.

Interventions
The imaging techniques being considered in this review are scintimammography, BSGI, and MBI. These procedures use radiotracers, which are injected intravenously, followed by nuclear medicine imaging, to detect abnormalities of the breast. Scintimammography uses planar imaging with the woman lying prone and the camera positioned laterally. If the area of interest includes the axilla, the camera can be positioned to include the axilla. During BSGI and MBI, the patient is seated in a position similar to mammography and the breast is lightly compressed. The differences between these techniques are the number and type of detectors used in the camera.

Scintimammography, BSGI, and MBI are administered in tertiary care centers or other facilities equipped with the gamma imaging technology.

Comparators
The following tests and practices are currently being used to make decisions about women with dense breasts or high-risk for breast cancer: mammography alone, ultrasonography, or MRI. The comparators are administered in facilities with specialized equipment.

Outcomes
True-positives can inform decisions to initiate treatment among newly diagnosed women with breast cancer.

False-positives may lead to unnecessary biopsies in women in need of a definitive diagnosis.
True-negatives may reduce the number of biopsies in women in need of a definitive breast cancer diagnosis.

False-negatives may prevent women from pursuing the necessary evaluations to determine a breast cancer diagnosis.

The time frame of interest for calculating performance characteristics is time to biopsy result. Patients who forgo biopsy based on test results could miss or delay the diagnosis of cancer. Years of follow-up would be necessary to determine the effects on overall survival (OS).

**Study Selection Criteria**
For the evaluation of the clinical validity of gamma imaging in women with dense breasts or at high-risk for breast cancer, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a 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).

Several observational studies have assessed BSGI or MBI in women at high-risk for breast cancer. With advances in imaging technology, lower doses of Tc 99m sestamibi are feasible. Lower doses of Tc 99m sestamibi were specifically used in MBI procedures in studies by Rhodes et al (2015) and Shermis et al (2016). Higher doses of Tc 99m sestamibi were initially used for BSGI in the Brem et al (2016) study, but lower doses were allowed for 196 patients after a protocol change.

### Table 1. Study Characteristics of Clinical Validity BSGI or MBI in Women With Dense Breasts or at High-Risk for Breast Cancer

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Population</th>
<th>Design</th>
<th>Reference Standard</th>
<th>Threshold for Positive Index Test</th>
<th>Timing of Reference and Index Tests</th>
<th>Blinding of Assessors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang (2020)</td>
<td>Women with heterogeneous or extremely dense breasts who underwent mammography plus either BSGI or ultrasonography</td>
<td>Retrospective</td>
<td>Surgery or core needle biopsy records</td>
<td>BI-RADS 4 or 5</td>
<td>Assessors blinded to previous analysis of BSGI</td>
<td></td>
</tr>
<tr>
<td>Shermis (2016)</td>
<td>Women with heterogeneous or extremely dense breasts and negative</td>
<td>Retrospective</td>
<td>Biopsy by ultrasonographic guidance (stereotactic or MRI-guided biopsy) when negative</td>
<td>BI-RADS 0, 3, 4, or 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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mammograms recommended for supplemental screening with MBI

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Enrolled N</th>
<th>Final N</th>
<th>Clinical Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brem (2016)²¹</td>
<td>Women at increased breast cancer risk undergoing BSGI for supplemental screening after negative or probably benign mammogram</td>
<td>Retrospective</td>
<td>Pathologic results of biopsy or follow-up imaging that did not demonstrate evidence of malignancy</td>
</tr>
<tr>
<td>Rhodes (2015)²²</td>
<td>Women with heterogeneously or extremely dense breasts who underwent mammography, MBI, or mammography in combination with MBI</td>
<td>Prospective</td>
<td>Histopathologic diagnosis from surgical excision or core needle biopsy</td>
</tr>
<tr>
<td>Rhodes (2011)²³</td>
<td>Women with heterogeneously or extremely dense breasts and at additional risk for breast cancer who underwent mammography, MBI, or mammography in combination with MBI</td>
<td>Prospective</td>
<td>Histopathologic diagnosis from surgical excision or core needle biopsy</td>
</tr>
<tr>
<td>Brem (2005)²⁴</td>
<td>Women at high risk for breast cancer with normal mammographic findings undergoing BSGI</td>
<td>Prospective</td>
<td>Biopsy</td>
</tr>
</tbody>
</table>

**Table 2. Results of Clinical Validity Studies of BSGI or MBI in Women With Dense Breasts or at High-Risk for Breast Cancer**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Enrolled N</th>
<th>Final N</th>
<th>Clinical Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang (2020)²⁵</td>
<td>364</td>
<td></td>
<td>Sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased by 25.23% with BSGI vs. 22.02% with ultrasonography (mean difference)</td>
</tr>
</tbody>
</table>

BI-RADS: Breast Imaging Reporting and Data System; BSGI: breast-specific gamma imaging; MBI: molecular breast imaging; MRI: magnetic resonance imaging
3.21% (p=0.23) in women with false-negative mammograms 10.27% (p=0.003) in women with false-positive mammograms 9.1% (95% CI, 5.4 to 15.0) as a result of 13 malignant lesions of 143 positive MBI findings

6.7% as a result of 14 malignancies per 212 abnormal BSGI findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shemis (2016)</td>
<td>1696</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mammography: 23.8% (95% CI, 10.6 to 45.1)</td>
<td>MBI: 81.0% (95% CI, 60.0 to 92.3)</td>
<td>MBI + mammography: 90.5% (95% CI, 71.1 to 97.3; p&lt;0.001 vs. mammography alone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mammography: 89.1% (95% CI, 87.5 to 90.6)</td>
<td>MBI: 93.5% (95% CI, 92.1 to 94.6)</td>
<td>MBI + mammography: 83.4% (95% CI, 81.4 to 85.1; p&lt;0.001 vs. mammography alone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MBI + mammography: 83.4% (95% CI, 81.4 to 85.1; p&lt;0.001 vs. mammography alone)</td>
</tr>
<tr>
<td>Brem (2016)</td>
<td>849</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mammography: 2.9% (95% CI, 1.2 to 6.5)</td>
<td>MBI: 14.3% (95% CI, 9.1 to 21.7)</td>
<td>MBI + mammography: 6.8% (95% CI, 4.4 to 10.4; p=0.021 vs. mammography alone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MBI + mammography: 6.8% (95% CI, 4.4 to 10.4; p=0.021 vs. mammography alone)</td>
</tr>
<tr>
<td>Rhodes (2015)</td>
<td>1608</td>
<td>1585</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mammography: 27% (95% CI, 9.7 to 56.6)</td>
<td>MBI: 93% (95% CI, 91.3 to 94.5)</td>
<td>MBI + mammography: 85% (95% CI, 82.8 to 87.3; p&lt;0.001 vs. mammography alone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mammography: 91% (95% CI, 88.8 to 92.0)</td>
<td>MBI + mammography: 83.4% (95% CI, 81.4 to 85.1; p&lt;0.001 vs. mammography alone)</td>
<td>MBI + mammography: 85% (95% CI, 82.8 to 87.3; p&lt;0.001 vs. mammography alone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MBI + mammography: 85% (95% CI, 82.8 to 87.3; p&lt;0.001 vs. mammography alone)</td>
</tr>
<tr>
<td>Rhodes (2011)</td>
<td>1007</td>
<td>936</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mammography: 27% (95% CI, 9.7 to 56.6)</td>
<td>MBI: 93% (95% CI, 91.3 to 94.5)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Mammography: 91% (95% CI, 88.8 to 92.0)</td>
<td>MBI + mammography: 83.4% (95% CI, 81.4 to 85.1; p&lt;0.001 vs. mammography alone)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MBI + mammography: 85% (95% CI, 82.8 to 87.3; p&lt;0.001 vs. mammography alone)</td>
</tr>
<tr>
<td>Brem (2005)</td>
<td>94</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100% (95% CI, 22 to 100) based on 2 cancers in 16 positive BSGI findings</td>
<td>85% based on 78 negative BSGI findings in 92 patients without cancer</td>
<td>12.5% based on 78 negative BSGI findings in 92 patients without cancer</td>
<td></td>
</tr>
</tbody>
</table>

BSGI: breast-specific gamma imaging; CI: confidence interval; MBI: molecular breast imaging; NPV: negative predictive value; PPV: positive predictive value

Table 3: Study Relevance Limitations of Observational Studies of BSGI or MBI in Women With Dense Breasts or at High-Risk for Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang (2020)</td>
<td>22</td>
<td>1. Tc 99m sestamibi</td>
<td></td>
<td>3. Predictive values not reported</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4: Study Relevance Design and Conduct Limitations of Observational Studies of BSGI or MBI in Women With Dense Breasts or at High-Risk for Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Blinding&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Delivery of Test&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Selective Reporting&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Completeness of Follow-Up&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Statistical&lt;sup&gt;f&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Zhang (2020)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1. Assessors only blind to prior BSGI</td>
<td>1. Timing of histopathology not described</td>
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<td>Shermis (2016)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>1. Blinding not described</td>
<td>1. Timing of histopathology not described</td>
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<tr>
<td>Brem (2016)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>1. Not blinded</td>
<td>1. Timing of histopathology not described</td>
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<td>Rhodes (2015)&lt;sup&gt;19&lt;/sup&gt;</td>
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<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context for test is unclear; 3. Study population unclear; 4. Study population not representative of intended clinical use; 5. Study population is subpopulation of intended use

<sup>b</sup> Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not version currently in clinical use

<sup>c</sup> Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose

<sup>d</sup> Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests)

<sup>e</sup> Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease
Section Summary: Dense Breasts or High-Risk for Breast Cancer

Three prospective studies have compared the incremental difference in diagnostic accuracy when BSGI or MBI is added to mammography in women at increased risk, and both 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. Studies tended to include women at different risk levels (e.g., 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 from 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. A recent retrospective study in women with dense breasts compared the addition of ultrasonography or BSGI to mammography. The diagnostic accuracy was assessed by the area under the receiver operating characteristic curve revealing higher accuracy with mammography plus BSGI than mammography plus ultrasonography or mammography alone (area under the receiver operating characteristic curve 0.90 vs. 0.83 [p=0.0019] and 0.76, respectively).  

Indeterminate or Suspicious Breast Lesions

The following PICO was used to select literature to inform this review.

Patients

The population of interest is women with indeterminate or suspicious breast lesions, to confirm a diagnosis.

Interventions

The imaging techniques being considered in this review are scintimammography, BSGI, and MBI. (See explanation under the first indication.)

Comparators

The following tests and practices are currently being used to make decisions about women with indeterminate or suspicious breast lesions: mammography spot compression views, ultrasonography, or MRI. The comparators are administered in facilities with specialized equipment.
Outcomes
True-positives can inform decisions to initiate treatment among newly diagnosed women with breast cancer.
False-positives may lead to unnecessary biopsies in women in need of a definitive diagnosis. True-negatives may reduce the number of biopsies in women in need of a definitive breast cancer diagnosis.
False-negatives may prevent women from pursuing the necessary evaluations to determine a breast cancer diagnosis.

The time frame of interest for calculating performance characteristics is time to biopsy result. Patients who forgo biopsy based on test results could miss or delay the diagnosis of cancer. Years of follow-up would be necessary to determine the effects on overall survival (OS).

Study Selection Criteria
For the evaluation of the clinical validity of gamma imaging for indeterminate or suspicious breast lesions, studies that met the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a 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).

Cho et al (2016) retrospectively reviewed breast lesions in 162 women diagnosed with BI-RADS category 4 lesions (suspicious) on mammography or ultrasonography.25 Patients had subsequently undergone BSGI with Tc 99m sestamibi at 925 to 1110 MBq. 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 of 1 cm or smaller, the sensitivity of BSGI was 88.0% (95% CI, 68.6% to 97.5%) and the specificity was 86.8% (95% CI, 71.9% to 95.6%). For lesions larger 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%).

Meissnitzer et al (2015) in Austria evaluated BSGI in the diagnostic workup of 67 patients with 92 suspicious breast lesions identified on mammography and/or ultrasonography.26 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, 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%).

Tan et al (2014) 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.27 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.

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-positives in 408 of 420 breast cancer patients (sensitivity, 97%), including the detection 
of multifocal, multicentric disease and bilateral disease, and were false-negatives in 12 breast 
cancer patients. BSGI results were true-negatives 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. 
Hruska et al (2008) evaluated 150 patients with BI-RADS classification 4 or 5 lesions less than 2 cm 
identified on mammography or ultrasound who were scheduled for a biopsy. The patients 
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 of 1 
centimeter or less. Overall, MBI specificity (across patients) was 69%. The proportion of patients 
with cancer in this study was higher than might have been expected in a screening population 
with suspicious lesions on mammography. This was the case because preference was given to 
those who had a high suspicion of cancer or were likely to have a multifocal or multicentric 
disease.

Spanu et al (2008) evaluated 145 consecutive patients scheduled for biopsy with MBI (using Tc 
99m tetrofosmin) of suspected breast lesions. With an 86% prevalence of the disease, the 
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 avoiding biopsy but 
the NPV (83%) was not high enough to forgo biopsy.

Brem et al (2007) compared BSGI with MRI in 23 women who had 33 indeterminate 
lesions. Eight patients had 9 pathologically confirmed cancers. BSGI demonstrated a 
significantly greater specificity (71% [95% CI, 49% to 87%] vs. MRI [25% [95% CI, 11% to 47%] 
p<0.05) and comparable sensitivity (BSGI, 89% [95% CI, 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 likely was due to the small number of cancers in the 
study.

**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 utility of BSGI in evaluating indeterminate or suspicious lesions must be compared with 
other modalities that would be used (e.g., 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**

The following PICO was used to select literature to inform this review.
Patients
The relevant population of interest is women with breast cancer undergoing an evaluation to
detect any residual tumor tissue following neoadjuvant therapy.

Interventions
The imaging techniques being considered in this review are scintimammography and BSGI.
These procedures use radiotracers, which are injected intravenously, followed by nuclear
imaging, to detect abnormalities of the breast. Scintimammography uses planar imaging with
the woman lying prone and the camera positioned laterally. If the area of interest includes the
axilla, the camera can be positioned to include the axilla. During BSGI, the patient is seated in a
position similar to mammography and the breast is lightly compressed. The differences between
these techniques are the number and type of detectors used in the camera.

Scintimammography and BSGI are administered in facilities equipped with the gamma imaging
technology.

Comparators
The following tests and practices are currently being used by indication to make decisions about
women with breast cancer undergoing screening to detect any residual tumor tissue following
neoadjuvant therapy: MRI, fluorine 18 fluorodeoxyglucose positron emission tomography, or
ultrasonography. These comparators are administered facilities with specialized equipment.

Outcomes
True-positives can inform surgical and other management decisions.
False-positives may lead to unnecessary treatment.

True-negatives can inform surgical and other management decisions.
False-negatives may result in incorrect treatment decisions.

For women already diagnosed with breast cancer who are using the tests to guide treatment
decisions, years of follow-up are necessary to capture recurrence rates and survival rates.

Study Selection Criteria
For the evaluation of the clinical validity of gamma imaging for detection of residual tumor after
neoadjuvant therapy, studies that met the following eligibility criteria were considered:
• Reported on the accuracy of the marketed version of the technology (including any
  algorithms used to calculate scores)
• Included a suitable reference standard (describe the reference standard)
• Patient/sample clinical characteristics were described
• Patient/sample selection criteria were described.

Systematic Reviews
A systematic review and meta-analysis by Guo et al (2016) identified 14 studies investigating the
performance of BSGI with Tc 99m 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 one 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%).

Retrospective Studies
The largest study included in the Guo et al (2016) systematic review is the retrospective and
single-center by Lee et al (2014). 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 (i.e., either breast-conserving therapy [64%] or mastectomy [36%]). Of 122 patients, 104 (85%) had the residual disease by pathologic review. BSGI sensitivity was 74%, specificity was 72%, NPV was 33%, and PPV was 94%. The sensitivity of BSGI varied by cellularity and size of residual tumor (greater sensitivity with greater cellularity and greater tumor size).

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

Section Summary: Detection of Residual Tumor After Neoadjuvant Therapy
A systematic review of studies evaluating BSGI for detecting residual tumor after neoadjuvant therapy found a pooled sensitivity of 86% and a pooled specificity of 69%, compared with 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.

Disease Detection During Preoperative Planning for Breast-Conserving Surgery
The following PICO was used to select literature to inform this review.

Patients
The population of interest is women with breast cancer undergoing preoperative planning to determine eligibility for breast-conserving surgery.

Interventions
The imaging techniques being considered in this review are scintimammography and BSGI. (See explanation under the previous indication.) These interventions assess breast tumor characteristics to determine whether breast-conserving surgery is appropriate or whether a mastectomy is required to obtain adequate margins.

Scintimammography and BSGI are administered in tertiary care centers or other facilities equipped with gamma imaging technology.

Comparators
The following tests and practices are currently being used by indication to make decisions about women with breast cancer undergoing planning for breast-conserving surgery: MRI. MRIs are administered in facilities with specialized equipment.

Outcomes
True-positives can inform surgical and other management decisions. False-positives may lead to unnecessary treatment. True-negatives can inform surgical and other management decisions. False-negatives may result in incorrect treatment decisions. For women already diagnosed with breast cancer who are using the tests to guide treatment decisions, years of follow-up are necessary to capture recurrence rates and survival rates.

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 randomized controlled trials.

Edwards et al (2013) retrospectively assessed changes in the 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 a 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 re-excision because of positive surgical margins, and 14% and 6%, respectively, required a mastectomy. Based on this retrospective study, the clinical utility of BSGI for guiding surgical decision making in breast cancer patients would appear limited.

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

Scintimammography, Breast-Specific Gamma Imaging, and Radiopharmaceutical or Gamma Detection to Inform Treatment
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Clinical Context and Test Purpose
One purpose of scintimammography, BSGI, and radiopharmaceutical or gamma detection is to inform a treatment plan for women diagnosed with breast cancer. This review evaluates the use of these procedures among women with breast cancer undergoing screening to detect axillary metastases including those undergoing sentinel lymph node biopsy (SLNB)

The questions addressed in this evidence review:
- Does the use of scintimammography or BSGI improve the net health outcome compared with surgical nodal dissection in women with breast cancer undergoing screening to detect axillary metastases?
- Does the use of radiopharmaceutical and gamma detection improve the net health outcome compared with no testing in women with breast cancer who are undergoing SLNB to detect axillary metastases?
Detection of Axillary Metastases
The following PICO was used to select literature to inform this review.

Patients
The population of interest is women with breast cancer undergoing evaluation to detect axillary metastases.

Interventions
The imaging techniques being considered in this review are scintimammography and BSGI. (See explanation under the third indication.)

Scintimammography and BSGI are administered in tertiary care centers or other facilities equipped with gamma imaging technology.

Comparators
The following tests and practices are currently being used by indication to make decisions about women with breast cancer undergoing evaluation to detect any axillary metastases: surgical node dissection. Surgical node dissection is performed in a tertiary or other specialized facilities.

Outcomes
True-positives can inform surgical and other management decisions. False-positives may lead to unnecessary treatment.

True-negatives can inform surgical and other management decisions. False-negatives may result in incorrect treatment decisions.

For women already diagnosed with breast cancer who are using the tests to guide treatment decisions, years of follow-up are necessary to capture recurrence rates and survival rates.

Study Selection Criteria
For the evaluation of gamma imaging for the detection of axillary metastases, studies that met the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Systematic Reviews
Regarding the use of scintimammography to detect axillary metastases, a meta-analysis reviewed 45 studies of scintimammography and also reported summary estimates of 83% (95% CI, 82% to 84%) for sensitivity and 85% (95% CI, 83% to 86%) for specificity. In a review of studies published between 1994 and 1998, Taillefer (1999) showed a sensitivity of 77% and a specificity of 89%.

Case Series
Several case series using different radiopharmaceuticals have shown sensitivities in the high 80% to 90% range.

Section Summary: Detection of Axillary Metastases
Current evidence on BSGI for detection of axillary metastases includes 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 test is not accurate enough to replace surgical nodal dissection. No studies have examined patient outcomes comparing the use of scintimammography to aid in decision making regarding nodal dissection with going directly to nodal dissection.
Sentinel Lymph Node Biopsy for Detection of Axillary Metastases

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is women with breast cancer who are undergoing SLNB to detect axillary metastases.

Interventions
The therapy being considered is lymphoscintigraphy and radioactive localization for SLNB. Lymphoscintigraphy and radioactive localization are techniques that map sentinel nodes by identifying the lymph drainage basin, determining the number of sentinel nodes, differentiating the sentinel nodes, and marking the sentinel node over the skin for a biopsy.

Lymphoscintigraphy and radioactive localization are administered in tertiary care centers or other facilities equipped with gamma imaging technology.

Comparators
The following practice is currently being used to make decisions about detecting axillary metastases: injection of blue dye or indocyanine green fluorescence.

Outcomes
True-positives can inform surgical and other management decisions.
False-positives may lead to unnecessary treatment.
True-negatives can inform surgical and other management decisions.
False-negatives may result in incorrect treatment decisions.
For women already diagnosed with breast cancer who are using the tests to guide treatment decisions, years of follow-up are necessary to capture recurrence rates and survival rates.

Study Selection Criteria
For the evaluation of radiotracers for localization of sentinel lymph nodes, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Systematic Reviews
Pesek et al (2012) published a meta-analysis based on a search between 1993 and 2011; 183 articles met inclusion criteria (total N=9306 patients). This analysis examined the false-negative rate of SLNB in patients with breast cancer by localization technique: radioactive tracer alone, blue dye alone, or a combination of radioactive tracer and dye. The false-negative rate was highest for the dye-only group at 8.6% (95% CI, 6.7% to 10.8%) while the tracer-only group had a false-negative rate of 7.4% (95% CI, 5.6% to 9.3%), and the combination of dye-and-tracer had the lowest false-negative rate 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).

Thongvitokomarn et al (2020) published a meta-analysis comparing radioactive tracer or blue dye with indocyanine green fluorescence including 30 studies (N=4216 sentinel lymph node procedures). The analysis evaluated detection rate, number of sentinel lymph nodes removed, and the rate of positive tumors comparing indocyanine green, blue dye, and radioactive tracer. Overall lymph node detection rates (total number of patients whose sentinel lymph nodes were detected by each tracer divided by total number of patients administered each tracer) were
69% to 100%, 65.6% to 97.1%, and 85% to 100% with indocyanine green, blue dye, and radioactive tracer, respectively. The detection rate was significantly different between indocyanine green and blue dye (odds ratio, 6.73; 95% CI, 4.20 to 10.78) but not between indocyanine green and radiotracer imaging (odds ratio, 0.90; 95% CI, 0.40 to 2.03). The number of sentinel lymph nodes removed were 2.35, 1.92, and 1.72 indocyanine green, blue dye, and radioactive tracer, respectively. Tumor positive rates were calculated by dividing the number of pathological positive sentinel lymph nodes by the total number of sentinel lymph nodes detected by each tracer and analyzed from 8 studies; 8.5% to 20.7% with indocyanine green, 12.7% to 21.4% with blue dye, and 11.3% to 16% with radiotracer.

Goonawardena et al (2020) compared radioactive tracer to indocyanine green fluorescence for SLNB in early-stage breast cancer; 19 studies were included (N=2301). Overall lymph node detection rates ranged from 81.9% to 100% with indocyanine green fluorescence and 85% to 100% with radiotracer. Sentinel lymph node detection was not different between groups (odds ratio, 0.93; 95% CI, 0.47 to 1.83); there was heterogeneity between studies with I²=58%; p=0.003. Tumor positive detection (sensitivity) based on 11 studies were 65.2% to 100% and 76.9% to 100% for indocyanine green fluorescence and radiotracer, respectively. No difference in sensitivity was found (odds ratio, 1.17; 95% CI, 0.43 to 3.17); there was heterogeneity between studies with I²=41%; p=0.09.

Randomized Controlled Trials
A randomized study by van der Vorst et al (2012) compared Tc 99m radiotracer plus near-infrared fluorescence imaging using indocyanine green with or without the use of a patent blue dye for localization of sentinel lymph nodes. Twenty-four consecutive breast cancer patients who were all undergoing SLNB were studied. Of the 23 cases with successful sentinel lymph node mapping, the lymph nodes were both radioactive and fluorescent in 100% of cases, whereas only 84% of the 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.

Nonrandomized Trials
Johnson et al (2011) conducted a single institution study assessing 699 patients with operable breast cancer for SLNB. Using intraoperative Tc 99m-labeled 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 received radioactive colloid and isosulfan blue dye injections before axillary SLNB. 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 the use of a hand-held gamma detection probe of radioactive nodes during surgery.

Section Summary: Sentinel Lymph Node Biopsy for Detection of Axillary Metastases
For individuals who have breast cancer, are undergoing SLNB to detect any axillary metastases, and who have received radiopharmaceutical and gamma detection for localization of sentinel lymph nodes, the evidence includes 3 studies and 3 meta-analyses. These studies provide consistent evidence that diagnostic performance using radiopharmaceutical and gamma detection yields high success rates in identifying sentinel lymph nodes; further, these studies would suggest that diagnostic performance trends toward better detection rates using radiopharmaceutical as opposed to alternative methods using only blue dye, and similar detection rates with indocyanine green fluorescence.
Summary of Evidence

**Scintimammography, Breast-Specific Gamma Imaging, and Molecular Breast Imaging for Diagnosis**

For individuals who have dense breasts or high-risk for breast cancer who receive scintimammography, BSGI, or MBI as an adjunct to mammography, the evidence includes diagnostic accuracy studies. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, and treatment-related morbidity. Three prospective studies have assessed 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. A retrospective study found improved diagnostic accuracy and specificity with BSGI compared to ultrasonography when added to mammography. Studies of women at increased risk of breast cancer and negative mammograms found that a small number of additional cancers were detected. Studies tended to include women at different risk levels (e.g., women with dense breasts and those with BRCA1). Moreover, any potential benefits need to be weighed against the 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, BSGI, or MBI, the evidence includes diagnostic accuracy studies. Relevant outcomes are OS, disease-specific survival, test validity, and treatment-related morbidity. In the available studies, compared with biopsy, the negative predictive value 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 negative predictive value of BSGI (or MBI) would have to be extremely high to alter treatment decisions. The evidence to date does not demonstrate this level of negative predictive value. 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 OS, disease-specific survival, test 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 with 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 for disease detection, the evidence includes a retrospective observational study. Relevant outcomes are OS, disease-specific survival, test validity, and treatment-related morbidity. In the retrospective study, results suggested 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.

**Scintimammography and Breast-Specific Gamma Imaging for Treatment**

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 OS, disease-specific survival, test validity, and treatment-related morbidity. A meta-analysis of the available diagnostic accuracy studies found that the sensitivity and specificity of BSGI are 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.
Radiopharmaceutical and Gamma Detection for Treatment

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 3 meta-analyses. Relevant outcomes are OS, disease-specific survival, test validity, and treatment-related morbidity. Evidence indicates that using radiopharmaceutical and gamma detection for localization of sentinel lymph nodes yields high success rates in identifying sentinel lymph nodes; additionally, the diagnostic performance generally offers better detection rates with radiopharmaceutical than with the blue dye method and similar detection rates to indocyanine green fluorescence. 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 more favorable early results with reduced arm swelling and better quality of life. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Society of Nuclear Medicine

The Society of Nuclear Medicine (2010) released a procedure guideline on breast scintigraphy using breast-specific gamma cameras. The guideline was based on consensus, not on a systematic review of the literature or assessment of study quality, and most of it discusses procedures and specifications of the examination, documentation and recording, quality control, and radiation safety. The guidelines also listed common clinical indications for breast-specific gamma imaging but did not discuss the level of evidence for each indication.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2017) updated its 2011 practice bulletin on breast cancer screening in average-risk women. There was no discussion or recommendation for scintimammography or any other gamma imaging techniques for routine screening.

American College of Radiology

Appropriateness Criteria from the American College of Radiology rated breast-specific gamma imaging a 1 or 2 (indicating "usually not appropriate" for breast cancer screening), in patients with high or intermediate breast cancer risk (last reviewed in 2017), palpable breast masses (last reviewed in 2016), and workup of breast pain (last reviewed in 2018). New guidelines on screening for breast cancer in above average-risk patients (last reviewed in 2018) do not recommend the use of MBI for breast cancer screening in any higher-risk population. The guidelines state, “further advances in detector technology to allow lower dosing, more widespread penetration of MBI-guided biopsy capabilities, and additional large prospective trials (to include incidence screening results) will be needed before MBI can be embraced as a screening tool, even in women at elevated risk.”

American Society of Clinical Oncology

The American Society of Clinical Oncology (2016) reaffirmed its 2014 recommendations on the use of sentinel node biopsy for patients with early-stage breast cancer. The recommendations were based on randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines from 2012 through July 2016. The recommendations included:

"Women without sentinel lymph node (SLN) metastases should not receive axillary lymph node dissection (ALND). Women with 1 to 2 metastatic SLNs who are planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo ALND (in most cases). Women with SLN metastases who will undergo mastectomy should be offered ALND. These 3 recommendations are based on randomized controlled trials. Women with operable breast cancer and multicentric tumors, with ductal carcinoma in situ, who will undergo mastectomy, who previously underwent breast and/or axillary surgery, or who received
preoperative/neoadjuvant systemic therapy may be offered SNB [sentinel node biopsy]. Women who have large or locally advanced invasive breast cancer (tumor size T3/T4), inflammatory breast cancer, or ductal carcinoma in situ (when breast-conserving surgery is planned) or are pregnant should not undergo SNB."

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network's guidelines (v.4.2020) on invasive breast cancer with clinical stage I, IIA, IIB, and IIIA T3, N1, M0 (BINV-D) include sentinel node mapping and excision for clinically node-negative patients at time of diagnosis or following negative fine-needle aspiration or core biopsy of clinically positive nodes at time of diagnosis. If the sentinel nodes are found to be negative on pathologic examination, then no further axillary surgery is suggested (category 1 recommendation).

Network guidelines on breast cancer screening and diagnosis (v.1.2020) state: “Current evidence does not support the routine use of molecular imaging (e.g. breast-specific gamma imaging, sestamibi scan, or positron emission mammography) as screening procedures, but there is emerging evidence that these tests may improve detection of early breast cancers among women with mammographically dense breasts. However, the whole-body effective radiation dose with these tests is substantially higher than that of mammography.”

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**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 ongoing and unpublished trials that might influence this review are listed in Table 5.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td>NCT02324387</td>
<td>Tc99m Sestamibi Molecular Breast Imaging</td>
<td>100</td>
<td>Mar 2021</td>
</tr>
<tr>
<td>NCT02556684</td>
<td>A Prospective Study to Evaluate Dynamic Breast-Specific Gamma Imaging in Monitoring Tumor Responses in Patients With Locally Advanced Breast Cancer Undergoing Neoadjuvant Chemotherapy</td>
<td>200</td>
<td>Oct 2020</td>
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<tr>
<td>NCT02744053</td>
<td>Multimodality Breast Imaging for the Assessment of Tumor Response to Neoadjuvant Chemotherapy in Triple Negative Breast Cancer Patients</td>
<td>100</td>
<td>Nov 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**References**


**Documentation for Clinical Review**

*Please provide the following documentation:*
- History and physical and/or consultation notes including:
  - Name and reason for testing
- Mammogram report
Post Service (in addition to the above, please include the following):
- Procedure (imaging) report

**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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>78800</td>
<td>Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); planar, single area (e.g., head, neck, chest, pelvis), single day imaging <em>(Code revision effective 1/1/2020)</em></td>
</tr>
<tr>
<td>CPT</td>
<td>78801</td>
<td>Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); planar, 2 or more areas (e.g., abdomen and pelvis, head and chest), 1 or more days imaging or single area imaging over 2 or more days <em>(Code revision effective 1/1/2020)</em></td>
</tr>
<tr>
<td>CPT</td>
<td>78803</td>
<td>Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT), single area (e.g., head, neck, chest, pelvis), single day imaging <em>(Code revision effective 1/1/2020)</em></td>
</tr>
<tr>
<td>HCPCS</td>
<td>A4641</td>
<td>Radiopharmaceutical, diagnostic, not otherwise classified</td>
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<tr>
<td>HCPCS</td>
<td>A9500</td>
<td>Technetium tc-99m sestamibi, diagnostic, per study dose</td>
</tr>
<tr>
<td>HCPCS</td>
<td>A9502</td>
<td>Technetium Tc-99m tetrofosmin, diagnostic, per study dose</td>
</tr>
<tr>
<td>HCPCS</td>
<td>A9520</td>
<td>Technetium tc-99m, tilmanocept, diagnostic, up to 0.5 millicuries</td>
</tr>
<tr>
<td>HCPCS</td>
<td>A9541</td>
<td>Technetium Tc-99m sulfur colloid, diagnostic, per study dose, up to 20 millicuries</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S8080</td>
<td>Scintimammography (radioimmunoscintigraphy of the breast), unilateral, including supply of radiopharmaceutical</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>
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<tbody>
<tr>
<td>02/25/1998</td>
<td>Adopted policy from BCBSA TEC</td>
</tr>
<tr>
<td>11/02/2002</td>
<td>Coding Update</td>
</tr>
<tr>
<td>01/07/2011</td>
<td>Policy title change from Scintimammography</td>
</tr>
<tr>
<td>01/08/2011</td>
<td>Policy revision with no position change</td>
</tr>
<tr>
<td>06/30/2015</td>
<td>Coding update</td>
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<tr>
<td>10/30/2015</td>
<td>Policy title change from Scintimammography/Breast-Specific Gamma Imaging/Molecular Breast Imaging</td>
</tr>
<tr>
<td>03/01/2017</td>
<td>Policy revision with position change</td>
</tr>
<tr>
<td>11/01/2017</td>
<td>Policy revision without position change</td>
</tr>
</tbody>
</table>
### Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member’s illness, injury, or disease.

**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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 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.