This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Treatment-related morbidity</td>
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Description

Scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (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 one or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer.

Summary of Evidence

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 three 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 (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. 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 negative predictive value (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 one 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 three 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 three 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 (e.g., 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 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.

**Policy**

Scintimammography, breast-specific gamma imaging and molecular breast imaging 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.

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

**Policy Guidelines**

The most commonly-used radiopharmaceutical in BSGI or MBI is technetium 99m (Tc-99m) sestamibi (marketed by Draxis Specialty Pharmaceuticals, Cardinal Health 414, Mallinckrodt, and Pharmalucence).

The 2013 Breast Imaging Reporting and Data System (BI-RADS) breast assessment and breast tissue categories are in Table PG1
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 (e.g., less than 15 mm), because of the relatively poor resolution of conventional gamma cameras in imaging the breast.

BSGI 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 (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 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.2

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. 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 eight-year Kaplan-Meier estimates.3 Moreover, additional three-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.5 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 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.”6

Technetium TC-99m tetrofosmin (Myoview™), a gamma-emitter used in some BSGI studies,7, 8 is approved by the Food and Drug Administration only for cardiac imaging.9

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).10 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

Scintimammography, BSGI, and MBI

The radiation dose associated with BSGI is substantial for diagnostic breast imaging modalities. According to Appropriateness Criteria from American College of Radiology (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.11 According to ACR, 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.12 The authors compared this dose with the estimated annual background radiation, which varies world-
wide between 2.5 – 10 mSv and asserted that the effective dose from MBI “is considered safe for use in routine screening.”

A 2010 article 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).13 The author, 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 VII report14 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 to 82 per 100,000 for BSGI (depending on the dose of Tc 99m sestamibi), and
- 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 to 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 it is used synonymously with the term breast-specific gamma camera, as used in this Protocol.

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

Regulatory Status

Several scintillation (gamma) cameras have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for “measuring and imaging the distribution of radionuclides in the human body by means of photon detection.”15 Examples of gamma cameras used in breast-specific gamma imaging are the 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 FDA through the NDA process (NDA 017858) for use as an injection to localize lymph nodes in breast cancer patients.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


