



BlueCross BlueShield
of Alabama

Name of Blue Advantage Policy:

Scintimammography and Gamma Imaging of the Breast and Axilla

Policy #: 452

Latest Review Date: September 2023

Category: Radiology

BACKGROUND:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

- 1. Safe and effective;*
- 2. Not experimental or investigational*;*
- 3. Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
 - Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - Furnished in a setting appropriate to the patient's medical needs and condition;*
 - Ordered and furnished by qualified personnel;*
 - One that meets, but does not exceed, the patient's medical need; and*
 - At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **scintimammography, breast-specific gamma imaging and molecular breast imaging** as a **non-covered** benefit and as **investigational** in all applications, including but not limited to their use as an adjunct to mammography or in staging the axillary lymph nodes.

Blue Advantage will treat the **use of gamma detection following radiopharmaceutical administration for localization of sentinel lymph nodes** in individuals with breast cancer as a **covered benefit**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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 the use of differing gamma camera technology which may improve diagnostic performance for detecting small lesions. 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.

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 (NPV), and can preclude the need for biopsy. Additional imaging for asymptomatic women who have dense breasts and negative mammograms has been suggested, but the best approach is subject to debate.

Scintimammography

Scintimammography is a diagnostic modality using radiopharmaceuticals to detect tumors of the breast. After intravenous injection of a radiopharmaceutical, the breast is evaluated with 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., smaller than 15mm) because of the relatively poor resolution of conventional gamma cameras in imaging the breast.

Breast-Specific Gamma Imaging

Breast-specific gamma imaging (BSGI) and molecular breast imaging (MBI) were developed to address this issue. Breast-specific gamma cameras acquire images while the patient is seated in a position similar to mammography and the breast is lightly compressed. Detector heads are immediately next to the breast, increasing resolution, and the images can be compared with the mammographic images. Breast-specific gamma imaging and molecular breast imaging differ primarily in the type and number of detectors used (e.g., multi-crystal arrays of cesium iodide or sodium iodide, or non-scintillating, 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. The radiotracer typically used is technetium Tc-99m sestamibi. MBI imaging takes approximately 40 minutes.

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 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 8-year Kaplan-Meier estimates. Additional 3-year follow-up of morbidity after surgical node dissection revealed lower morbidity in the SLND group, including lower rates of arm swelling, numbness, tingling, and fewer early shoulder abduction deficits. 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 to 1.19), no significant difference in disease-free survival (HR=0.83; 95% CI, 0.60 to 1.14), and similar rates of locoregional recurrence. However, axillary node dissection was associated with significantly greater surgical morbidity (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 technetium-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 U.S. Food and Drug Administration (FDA)-approved only for cardiac imaging.

Lymphoscintigraphy and/or Hand-Held Gamma Detection of Sentinel Lymph Nodes

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

Radiation Exposure

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

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

According to a 2015 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 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 to 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). The author of this study, a consultant to GE Healthcare and a member of the medical advisory boards of Koning (manufacturer of dedicated breast computed tomography [CT]) and Bracco (MR contrast agents), used group risk estimates from the Biological Effects of Ionizing Radiation (BEIR) VII report to assess the risk of radiation-induced cancer and mortality from breast imaging studies. For a patient with average-sized breasts (compressed thickness during mammography of 5.3 cm per breast), estimated LARs of cancer at age 40 were:

- 5 per 100,000 for digital mammography (breast cancer only),
- 7 per 100,000 for screen film mammography (breast cancer only),

- 55 to 82 per 100,000 for BSGI (depending on the dose of technetium Tc-99m sestamibi), and
- 75 for 100,000 for PEM.

Corresponding lifetime attributable risks 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 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.

Although the use of BSGI (or MBI) has been proposed for women at high-risk of breast cancer, there is controversy and speculation over whether some women (eg, those with BRCA variants) have a heightened radiosensitivity. If women with BRCA variants are more radiosensitive than the general population, studies may underestimate the risks of breast imaging with ionizing radiation (i.e., mammography, BSGI, MBI, positron emission mammography, single-photon emission computed tomography/computed tomography, breast-specific computed tomography, tomosynthesis) in these women. In contrast, ultrasonography and magnetic resonance imaging (MRI) do not use radiation. More research is needed to resolve this issue. Also, the risk associated with radiation exposure will be greater for women at high-risk of breast cancer, whether or not they are more radiosensitive because they start screening at a younger age when the risks associated with radiation exposure are greater. In addition, a large, high-quality, head-to-head comparison of BSGI (or MBI) and MRI would be needed, especially for women at high-risk of breast cancer, because MRI, alternated with mammography, is currently the recommended screening technique.

Notes: The term “molecular breast imaging” is used in different ways, sometimes for any type of breast imaging involving molecular imaging, including positron emission mammography (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 (SPECT) and positron emission tomography (PET) of the breast are not covered in this review.

KEY POINTS:

The most recent literature review was updated through August 23, 2023.

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, 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. 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 that the technology results in an improvement in the net health outcome.

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 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 that the technology results in an improvement in the net health outcome.

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 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 that the technology results in an improvement in the net health outcome.

For individuals who have breast cancer undergoing surgical planning for breast-conserving therapy who receive scintimammography and BSGI, the evidence includes a retrospective observational study. Relevant outcomes are overall survival, disease-specific survival, test 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 that the technology results in an improvement in the net health outcome.

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 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 that the technology results in an improvement on the health outcome.

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 a randomized controlled trial, nonrandomized studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related morbidity. A meta-analysis and three additional studies provide evidence that using radiopharmaceutical and gamma detection for localization of sentinel lymph nodes yield high success rates in identifying sentinel lymph nodes; additionally, the diagnostic performance generally offers better detection rates using radiopharmaceutical than with alternative methods using only blue dye. The evidence indicates 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 an improvement in the net health outcome.

Practice Guidelines, and Position Statements

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). Guidelines on screening for breast cancer in above average-risk patients (last reviewed in 2018) do not recommend the use of molecular breast imaging (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." In a 2021 guideline for supplemental breast

cancer screening based on breast density, MBI is categorized as "usually not appropriate" regardless of breast density and breast cancer risk.

American Society of Clinical Oncology

In 2016, the American Society of Clinical Oncology reaffirmed its 2014 recommendations on the use of sentinel node biopsy (SNB) 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 one to two 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 three 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. 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 guidelines (v.4.2022) on breast cancer state that sentinel lymph node biopsy is the preferred method for axillary lymph node staging if the patient is a candidate for sentinel lymph node biopsy. If the sentinel nodes are found to be negative on pathological examination, then no further axillary surgery is suggested.

Network guidelines on breast cancer screening and diagnosis include the following relevant recommendations:

“There is emerging evidence that breast scintigraphy and contrast-enhanced mammography may improve detection of early breast cancers among females with mammographically dense breasts; current evidence does not support their routine use as alternative screening procedures.”

“Consider contrast-enhanced mammography (CEM) or molecular breast imaging (MBI) whole breast ultrasound for those who qualify for but cannot undergo MRI. Whole breast ultrasound may be done if contrast-enhanced imaging or functional imaging is not available/accessible.”

High-Risk Individuals

- “In high-risk settings, based on current evidence and considering the FDA safety announcement (gadolinium-based contrast agents), we continue to recommend annual MRI in select populations after shared decision-making. Breast cancer screening MRI may also increase recall and increase benign breast biopsies.

- Abbreviated MRI has a higher cancer detection rate than mammography with tomosynthesis and likely has similar sensitivity compared to full diagnostic protocol breast MRI.
- CEM and MBI are also options for higher risk breast cancer screening. CEM has the risk of iodinated contrast reactions and has a higher breast radiation exposure per exam than standard mammography. MBI has a whole-body effective radiation dose substantially higher than that of mammography.

U.S. Preventive Services Task Force Recommendations

Not applicable.

KEY WORDS:

Scintimammography, breast-specific gamma imaging, BSGI, molecular breast imaging, MBI, Miraluma® Dilon 6800® LumaGEM™, RadioGenix™ System

APPROVED BY GOVERNING BODIES:

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

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

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

Technetium-99m-sulfur colloid was approved by FDA through the new drug application (GE Healthcare, NDA 017456; Mallinckrodt, NDA 017724) process although these products appear to be no longer 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.

In 2018, 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.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

78195	Lymphatics and lymph node imaging
78800	Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); limited area
78801	Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); multiple areas
78803	Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); tomographic (SPECT), single area (e.g., head, neck, chest, pelvis), single day imaging

HCPCS Codes:

S8080	Scintimammography (radioimmunosintigraphy of the breast), unilateral, including supply of radiopharmaceutical
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POLICY HISTORY:

Adopted for Blue Advantage, October 2010

Available for comment: October 20 through December 6, 2010

Medical Policy Group, June 2012

Medical Policy Group, June 2013

Medical Policy Group, June 2014

Available for comment June 23 through August 6, 2014

Medical Policy Group, June 2015

Medical Policy Group, October 2016

Available for comment October 26 through December 10, 2016

Medical Policy Group, October 2017

Medical Policy Group, October 2018 (7): Updates to Description, Key Points, Approved by Governing Bodies & References. Added Key Words: "RadioGenix™ System". No change in policy statement.

Medical Policy Group, October 2019

Medical Policy Group, September 2020

Medical Policy Group, October 2021

Medical Policy Group, September 2022

Medical Policy Group, September 2023

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.