Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Scintimammography and Gamma Imaging of the Breast and Axilla

Description/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 (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.[1]

SCINTIMAMMOGRAPHY

Scintimammography is a diagnostic modality using radiopharmaceuticals to detect tumors of the breast. 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. Scintimammography using conventional imaging modalities has relatively poor sensitivity in detecting smaller lesions (e.g., smaller than 15 mm), 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 that in mammography, and the breast is lightly compressed. Detector heads are immediately next to the breast, increasing resolution, and the images can be compared with mammographic images. BSGI and MBI differ primarily in the number and type of detectors used (e.g., multi-crystal arrays of cesium iodide or sodium iodide, or nonscintillating, semiconductor materials, such as cadmium zinc telluride [CZT]). 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]

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 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.[3] Additional 3-year follow-up of morbidity after surgical node dissection revealed lower morbidity in the SLND group, including lower rates of arm swelling, numbness, tingling, and fewer early shoulder abduction deficits.[4] A recent systematic review and meta-analysis by Ram et al (2014) reported no significant difference in overall survival (hazard ratio [HR], 0.94; 95% confidence interval [CI], 0.79 to1.19), no significant difference in disease-free survival (HR=0.83; 95% CI, 0.60 to 1.14), and similar rates of locoregional recurrence.[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, Breast Specific Gamma Imaging (BSGI), and Molecular Breast Imaging (MBI)

The primary radiopharmaceutical used with BSGI or MBI is technetium Tc-99m sestamibi (marketed by Draxis Specialty Pharmaceuticals Inc.; Cardinal Health 414, Mallinckrodt and Pharmalucence). 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 FDA-approved only for cardiac imaging.[9]

Lymphoscintigraphy and/or Hand-Held Gamma Detection 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 the 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.[11] According to the ACR Appropriateness Criteria, at these levels BSGI is not indicated for breast cancer screening.

According to another study by Hruska and O'Connor (who report receiving royalties from licensed technologies by an agreement with Mayo Clinic and Gamma Medica), the effective dose from a lower "off-label" administered dose of 240-300 MBq (6.5-8 mCi) of Tc- 99m sestamibi that is made feasible with newer dual-head MBI systems, is 2.0-2.5 mSv. For comparison, the effective dose (i.e., mean glandular dose) of digital mammography is estimated to be about 0.5 mSv. However, it is important to note that the dose for MBI is given to the entire body.[12] The authors compared this dose with the estimated annual background radiation, which varies worldwide between 2.5 – 10 mSv and asserted that the effective dose from MBI "is considered safe for use in routine screening."

Hendrick (2010) calculated mean glandular doses, and lifetime attributable risk (LAR) of cancer due to film mammography, digital mammography, BSGI, and positron emission mammography (PEM).[13] The author, who is a consultant to GE Healthcare and a member of the medical advisory boards of Koning (manufacturer of dedicated breast computed tomography [CT]) and Bracco (MR contrast agents), used group risk estimates from the Biological Effects of Ionizing Radiation (BEIR) VII report[14] to assess the risks of radiation-induced cancer incidence and mortality from breast imaging studies. For a patient with the average-sized breast (compressed thickness during mammography of 5.3 cm per breast, estimated LARs of cancer at age 40 were:

- 5 per 100,000 for digital mammography (breast cancer only),
- 7 per 100,000 for screen film mammography (breast cancer only),
- 55-82 per 100,000 for BSGI (depending on the dose of technetium Tc99m 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),
- 26-39 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 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 (e.g., those with BRCAvariants) have a heightened radiosensitivity.[15,16] 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 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.

NOTE: 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 limited to imaging with a type of breast-specific gamma camera, as used in this policy.

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

Regulatory Status

Several scintillation (gamma) cameras have general 510(k) marketing clearance from FDA, which states that they are cleared for “measuring and imaging the distribution of radionuclides in the human body by means of photon detection.”[15] Two examples of gamma cameras used in BSGI or MBI (FDA Product Code IYX) are Dilon 6800® (Dilon Technologies, Newport News, VA) and 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.

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.

Medical Policy Statement

Scintimammography, breast-specific gamma imaging (BSGI) and molecular breast imaging (MBI) are considered experimental/investigational for all applications, including but not limited to their use as adjuncts to mammography or in staging the axillary lymph nodes. They have not been scientifically demonstrated to improve patient clinical outcomes.

The safety and effectiveness of localization of sentinel lymph nodes using radiopharmaceutical and gamma detection has been established. It may be considered a useful therapeutic or diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

Localization of sentinel lymph nodes using radiopharmaceutical and gamma detection may be useful for individuals who have breast cancer undergoing sentinel lymph node biopsy for detection of axillary metastases.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

76499*

Other codes (investigational, not medically necessary, etc.):

S8080

*when criteria is met

Rationale

This topic was the focus of a 2013 TEC Assessment.[16] However, lymphoscintigraphy and radioactive localization for sentinel lymph node biopsy were not included in scope for the TEC Assessment. A few studies reported on change in patient management after imaging, but there were insufficient data to determine whether these changes led to improvement in health outcomes. A subsequent 2013 TEC Special Report[1] 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.

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 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 are:

1. 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 high risk for breast cancer?
2. 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?
3. 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?
4. 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**s were used to select literature to inform this review.

Populations

The relevant populations of interest are women with dense breasts or 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.

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
The general outcomes of interest are overall survival (OS), disease-specific survival, test validity, and treatment-related morbidity.

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, 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

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).

Review of Evidence

Observational Studies

Several observational studies have assessed BSGI and 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).[19,20] 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.[21]

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

Author (Year)	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Zhang (2020)[22]	Women with heterogeneously or extremely dense breasts who underwent mammography plus either BSGI or ultrasonography	Retrospective	Surgery or core needle biopsy records	BI-RADS 4 or 5		Assessors blinded to previous analysis of BSGI
Shermis (2016)[20]	Women with heterogeneously or extremely dense breasts and negative mammograms recommended for supplemental screening with MBI	Retrospective	Biopsy by sonographic guidance (stereotactic or MRIguided biopsy when not visible by ultrasound)	BI-RADS 0, 3, 4, or 5		
Brem (2016)[21]	Women at increased breast cancer risk undergoing BSGI for supplemental screening after negative or probably benign mammogram	Retrospective	Pathologic results of biopsy or follow-up imaging that did not demonstrate evidence of malignancy	BI-RADS 0, 4, or 5		Assessors were not blind to patient history or adjunct imaging studies
Rhodes (2015)[19]	Women with heterogeneously or extremely dense breasts who underwent mammography, MBI, or mammography	Prospective	Histopathologic diagnosis from surgical excision or core needle biopsy	BI-RADS 3 to 4	365 days	MBI assessors blind to mammographic and clinical information

	in combination with MBI					
Rhodes (2011)[23]	Women with heterogeneously or extremely dense breasts and at additional risk for breast cancer who underwent mammography, MBI, or mammography in combination with MBI	Prospective	Histopathologic diagnosis from surgical excision or core needle biopsy	BI-RADS 0, 4 or 5	365 days	Assessors blind to other radiographic and clinical information
Brem (2005)[24]	Women at high risk for breast cancer with normal mammographic findings undergoing BSGI	Prospective	Biopsy	BI-RADS 4 to 5		BSGI assessors blind to mammographic and clinical information

BI-RADS: Breast Imaging Reporting and Data System; BSGI: breast-specific gamma imaging; MBI: molecular breast imaging; MRI: magnetic resonance imaging

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

Author (Year)	Enrolled N	Final N	Clinical Validity			
			Sensitivity	**Specificity**	**PPV**	**NPV**
Zhang (2020)[22]		364	Increased by 25.23% with BSGI vs. 22.02% with ultrasonography (mean difference 3.21%; p=0.23) in women with false negative mammograms	Increased by 30.82% with BSGI vs. 20.55% with ultrasonography (mean difference 10.27%; p=0.003) in women with false positive mammograms		
Shermis (2016)[20]		1696			9.1% (95% CI, 5.4 to 15.0) as a result of 13 malignant lesions of 143 positive MBI findings	
Brem (2016)[21]		849			6.7% as a result of 14 malignancies per 212 abnormal BSGI findings	

Rhodes (2015)[19]	1608	1585	Mammography: 23.8% (95% CI, 10.6 to 45.1) MBI: 81.0% (95% CI, 60.0 to 92.3) MBI + mammography: 90.5% (95% CI, 71.1 to 97.3; p<0.001 vs. mammography alone)	Mammography: 89.1% (95% CI, 87.5 to 90.6) MBI: 93.5% (95% CI, 92.1 to 94.6) MBI + mammography: 83.4% (95% CI, 81.4 to 85.1; p<0.001 vs. mammography alone)	Mammography: 2.9% (95% CI, 1.2 to 6.5) MBI: 14.3% (95% CI, 9.1 to 21.7) MBI + mammography: 6.8% (95% CI, 4.4 to 10.4; p=0.021 vs. mammography alone)	Mammography: 98.9% (95% CI, 98.2 to 99.3) MBI: 99.7% (95% CI, 99.3 to 99.9) MBI + mammography: 99.8% (95% CI, 99.4 to 100; p<0.001 vs. mammography alone)
Rhodes (2011)[23]	1007	936	Mammography: 27% (95% CI, 9.7 to 56.6) MBI: 82% (95% CI, 52.3 to 94.9) MBI + mammography: 91% (95% CI, 62.3 to 98.4; p<0.016 vs. mammography alone)	Mammography: 91% (95% CI, 88.8 to 92.0) MBI: 93% (95% CI, 91.3 to 94.5) MBI + mammography: 85% (95% CI, 82.8 to 87.3; p<0.001 vs. mammography alone)	Mammography: 3% (95% CI, 1.2 to 9.6) MBI: 12% (95% CI, 6.6 to 21.8) MBI + mammography: 8% (95% CI, 4.3 to 13.1; p=0.158 vs. mammography alone)	
Brem (2005)[24]	94	94	100% (95% CI, 22 to 100) based on 2 cancers in 16 positive BSGI findings	85% based on 78 negative BSGI findings in 92 patients without cancer	12.5% based on 2 cancers in 16 positive BSGI findings	100% based on 78 negative BSGI findings in 92 patients without cancer

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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Zhang (2020)[22]		1. Tc 99m sestamibi dosing undefined		3. Predictive values not reported 5. Adverse events of the test not described	
Shermis (2016)[20]				3. Sensitivity and specificity could not be calculated due to missing data 5. Adverse events of the test not described	
Brem (2016)[21]				3. Sensitivity and specificity not reported 5. Adverse events of the test not described	
Rhodes (2015)[19]				5. Adverse events of the test not described	

Rhodes (2011)[23]				5. Adverse events of the test not described	
Brem (2005)[24]				5. Adverse events of the test not described	

[a] 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
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not version currently in clinical use
[c] 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
[d] 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)
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease

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

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Zhang (2020)[20]		1. Assessors only blind to prior BSGI	1. Timing of histopathology not described			
Shermis (2016)[20]		1. Blinding not described	1. Timing of histopathology not described			2. No statistical tests to compare to alternatives
Brem (2016)[21]		1. Not blinded	1. Timing of histopathology not described			1.Confidence intervals not reported 2.No statistical tests to compare to alternatives
Rhodes (2015)[19]						
Rhodes (2011)[23]						
Brem (2005)[24]			1. Timing of histopathology not described			2. No statistical tests to compare to alternatives

[a] Selection: 1. Selection not described; 2. Selection not random nor consecutive (i.e., convenience)
[b] Blinding: 1. Not blinded to results of reference or other comparator tests
[c] Delivery of test: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described
[d] Selective reporting: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication
[e] Completeness of follow up: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data f Statistical: 1. Confidence intervals and/or p values not reported; 2. No statistical test reported to compare to alternatives

Section Summary: Dense Breasts or High Risk for Breast Cancer

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, and both the MBI studies were by the same research group. Sensitivity was higher with combined BSGI

(or MBI) and mammography, but specificity was lower. Studies of women at increased risk of breast cancer and negative mammograms found that a small number of additional cancers were detected. 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 to breast biopsy for false-negative findings. Even in studies that used a reduced dose of Tc-99m sestamibi, the effective dose (2.4 mSv) exceeded that of digital mammography (≈0.5 mSv) by a factor of 4.8. 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 ultrasound 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**s were used to select literature to inform this review.

Populations
The population of interest are 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.

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 timeframe 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 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.

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).

Review of Evidence
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 925 to 1110 MBq of Tc-99m sestamibi. Using biopsy-confirmed pathologic evaluation as the criterion standard, 66 (40.7%) of 162 lesions were found to be malignant. The sensitivity and specificity of BSGI were 90.9% (95% CI, 81.3% to 96.6%) and 78.1% (95% CI, 68.5% to 85.9%), respectively. The PPV was 74.1% (95% CI, 63.1% to 83.2%) and the NPV was 92.6% (95% CI, 84.6% to 97.2%). For lesions less than 1 cm, the sensitivity of BSGI was 88.0% (95% CI, 68.6% to 97.5%) and the specificity was 86.8% (95% CI, 71.9% to 95.6%). For lesions greater than 1 cm, the sensitivity was higher (92.7%; 95% CI, 80.1% to 98.5%) and the specificity was lower (61.5%; 95% CI, 44.6% to 76.6%).

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 ultrasound.[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 semi-quantitatively. Overall BSGI sensitivity and specificity were 90% and 56%, respectively, compared with ultrasound sensitivity and specificity of 99% and 20%, respectively. For lesions smaller than 1 cm, sensitivity of BSGI was 60%.

Tan et al (2014) assessed the diagnostic accuracy of dual-phase (at 10-15 minutes and at 90-120 minutes) BSGI 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 semi-quantitative 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 semi-quantitative analysis alone.

Spanu et al (2012) assessed the clinical impact of BSGI in a prospective study of 467 women with suspicious lesions on physical examination, MRI, ultrasound (US), or mammogram.[28] Histopathology reports were obtained in all cases. BSGI results were true positive in 408 of 420 (sensitivity, 97%), including the detection of multifocal, multicentric disease or bilateral disease, and were false negative in 12 breast cancer patients. BSGI results were true negative in 40 of 47 (specificity, 85%) patients with benign lesions. The authors calculated that BSGI provided additional value compared to mammography in 141 (30%) of 467 patients: 108 who had breast cancer and 33 with benign lesions.

Hruska et al (2008), 150 patients with BI-RADS classification 4 or 5 lesions smaller than 2 cm identified on mammography or ultrasound who were scheduled for biopsy. The patients underwent scintimammography using a dual-head, breast-specific gamma camera.[29] Results from three blinded readers were averaged. In 88 patients, 128 cancers were found. The per-lesion sensitivity with the dual-head camera was 90% (115/128) for all lesions and 82% (50/61) for lesions 1 cm or smaller. Overall, MBI specificity (by patient) was 69%. The proportion of patients with cancer in this study was higher than might be expected in a screening population with suspicious lesions on mammography. In selecting patients, preference was given to those who had high suspicion of cancer or who were likely to have multifocal or multicentric disease.

Spanu et al (2008) evaluated 145 consecutive patients scheduled for breast biopsy with MBI (using Tc-99m Tetrofosmin).[30] With an 86% prevalence of disease, sensitivity of BSGI was 98% per patient (100% for tumors larger than 10 mm and 91% for tumors 10 mm or smaller). Per-lesion specificity was 86%. Four cancers were missed, 3 of which were detected by mammography. The authors suggested using BSGI for surgical planning or to avoid biopsy, but the negative predictive value (NPV) of 83%was not high enough to forgo biopsy.

Brem et al (2007) compared BSGI and MRI in 23 women with 33 indeterminate lesions.[31] Eight patients had nine pathologically confirmed cancers. BGSI demonstrated a significantly greater specificity (71%, 95% CI: 49% to 87%) than MRI (25%, 95% CI: 11% to 47%; $p<0.05$). BSGI was comparable to MRI for 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 point out that the 100% sensitivity and 25% specificity of MRI is probably due to the small number of cancers in this study.

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, more effective therapy, or avoid unnecessary therapy or 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 RCTs. No direct evidence was identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Indeterminate or Suspicious Breast Lesions
A number of studies have evaluated the diagnostic accuracy of BSGI (or MBI) of suspicious lesions. Compared with biopsy, the NPV in studies that reported this outcome varied from 83% to 94%. The value of BSGI in evaluating indeterminate or suspicious lesions must be compared with other modalities that would be used (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**s were used to select literature to inform this review.

Populations
The relevant population of interest are 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.

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.

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 Tc-99m BSGI for evaluating the response to neoadjuvant therapy in patients with breast cancer.[32] 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 three 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).[33] 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 residual disease by pathologic review. BSGI sensitivity was 74%, specificity was 72%, NPV was 33%, and PPV was 94%. Sensitivity of BSGI varied with cellularity and size of residual tumor (greater sensitivity with greater cellularity and greater size).

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

Section Summary: Detection of Residual Tumor After Neoadjuvant Therapy

A 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 to histopathologic analysis. No studies were identified that compared the diagnostic accuracy of BSGI with other imaging approaches or that investigated the impact of BSGI on patient management decisions or health outcomes.

DISEASE DETECTION DURING PREOPERATIVE PLANNING FOR BREAST-CONSERVING THERAPY

The following **PICO**s were used to select literature to inform this review.

Populations

The population of interest are 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.

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.

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 surgical management of 218 women who had breast cancer and were eligible for breast-conserving therapy.[34] All patients had undergone preoperative BSGI or breast MRI. Twelve percent of patients who had BSGI and 29% of those who had MRI changed to mastectomy. On pathologic review, no patient who underwent mastectomy was eligible for breast-conserving therapy. Of patients who received breast-conserving therapy, 15% of those who had BSGI and 19% of those who had MRI required a single re-excision because of positive surgical margins, and 14% and 6%, respectively, required mastectomy. Based on this retrospective study, clinical utility of BSGI for guiding surgical decision making in breast cancer patients appears 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, it appeared as if 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

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**s were used to select literature to inform this review.

Populations

The population of interest are 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.)

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.

Outcomes

The general outcomes of interest are OS, disease-specific survival, test validity, and treatment-related morbidity.

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.[35] In a review of studies published between 1994 and 1998, Taillefer (1999) showed a sensitivity of 77% and specificity of 89%.[36]

Case Series
Several case series using different radiopharmaceuticals have shown sensitivities in the high 80% to 90% range.[37,38]

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**s were used to select literature to inform this review.

Populations
The relevant population of interest are 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.

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.

Review of Evidence

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).[39] This analysis examined the false-negative rate (FNR) of sentinel node biopsy in patients with breast cancer by localization technique: radioactive tracer alone, dye alone, or combination of radioactive tracer and dye. The FNR was highest for dye-only group at 8.6% (95% CI, 6.7% to 10.8%) while the tracer-only group had FNR of 7.4% (95% CI, 5.6% to 9.3%), and the combination of dye-and-tracer had the lowest FNR at 5.9% (95% CI, 4.8% to 7.1%) The Q-statistic for heterogeneity indicated that the three groups were not all equal (p=0.050). Subsequent pair wise 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).[40] 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).[41] 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

I^2=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 I^2=41%; p=0.09.

Randomized Controlled Trials

A randomized study by van der Vorst et al (2012) compared Tc-99m radiotracer combined with near-infrared fluorescence imaging using indocyanine green with or without use of patent blue dye for localization of sentinel lymph nodes.[42] Twenty-four consecutive breast cancer patients who were all undergoing sentinel lymph node biopsy were studied. Of the 23 cases where sentinel lymph node mapping was successful, the sentinel lymph nodes were both radioactive and fluorescent in 100% of cases, whereas only 84% of the sentinel lymph nodes showed blue dye staining. In addition, for 25% of cases, the gamma probe was needed to identify and locate the sentinel nodes during the first 15 minutes of localization.

Nonrandomized Trials

Johnson et al (2011) reported a single institution study assessing 699 patients with operable breast cancer for sentinel lymph node biopsy.[43] Using intraoperative Tc-99m-labelled radiopharmaceutical tracer subareolar injection, the sentinel node was localized in 98.6% of cases.

Martin et al (2000) reported a prospective multi-institutional study examining 758 patients who were clinical stage T1-2, N0, M0 invasive breast cancer and who had injection of both radioactive colloid and isosulfan blue dye before axillary sentinel lymph node biopsy.[44] 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.[45-47] Note that lymphoscintigraphy uses planar or tomographic imaging that differs from use of hand-held gamma detection probe of radioactive nodes during surgery.

Section Summary: SLNB for Detection of Axillary Metastases

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 3 meta-analyses. These studies provide consistent evidence that diagnostic performance using radiopharmaceutical and gamma detection for localization of sentinel lymph nodes yield high success rates in identifying sentinel lymph nodes and trend toward better detection rates using radiopharmaceutical compared to alternative methods using only blue dye, and similar detection rates with indocyanine green fluorescence.

SUMMARY OF EVIDENCE

Scintimammography, BSGI, and MBI for Diagnosis

For individuals who have dense breasts or high risk for breast cancer who receive scintimammography, breast-specific gamma imaging (BSGI) or molecular breast imaging (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. 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 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.

Scintimammography and BSGI 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 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 three studies and 3 meta-analyses. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. Evidence indicates that 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 than with blue dye methods and similar detection rates with 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might impact this policy are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02324387	Tc-99m Sestamibi molecular breast imaging	100	Mar 2022
NCT02556684	A Prospective Study to Evaluate Dynamic Breast-Specific Gamma Imaging in Monitoring Tumor Responses in Patients With Locally Advanced Breast Cancer Undergoing Neoadjuvant Chemotherapy	200	Oct 2020
NCT02744053	Multimodality breast imaging for the assessment of tumor response to neoadjuvant chemotherapy in triple negative breast cancer patients.	100	Dec 2022

NCT: national clinical trial

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Obstetricians and Gynecologists

In 2017 the American College of Obstetricians and Gynecologists replaced the 2011 practice bulletin on breast cancer screening in average-risk women.[48] There is 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),[11] palpable breast masses (last reviewed in 2017),[50] and workup of breast pain (last reviewed in 2018).[51] 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.”[52] 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.[532]

American Society of Clinical Oncology
In 2016 the American Society of Clinical Oncology reaffirmed the 2014 recommendations on the use of sentinel node biopsy (SNB) for patients with early-stage breast cancer.[53] The recommendations are based on randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines from 2012 through July 2016. The recommendations are:

“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 guideline (v.4.2023) on breast cancer state the 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 (category 1 recommendation).[54]

Network guidelines on breast cancer screening and diagnosis (v.1. 2023) state: "While there is emerging evidence that molecular imaging (breast-specific gamma imaging, sestamibi scan) as screening procedures may improve detection, whole-body effective radiation dose with these tests is substantially higher than that of mammography."[55.]

U.S. Preventive Services Task Force Recommendations
Not applicable.

Government Regulations
National/Local:

There is no national or local Michigan coverage determination on this topic. S8080 is not a valid code for Medicare.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Magnetic Resonance Imaging (MRI) of the Breast
- PET Scans: Oncologic Applications

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 2023, the date the research was completed.

Joint BCBSA/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
6/16/03	6/16/03	6/16/03	Joint medical policy established.
1/24/05	1/24/05	1/11/05	Routine review of non-covered service (changed from investigational to not medically necessary)
11/1/07	8/21/07	10/30/07	Routine review of non-covered service (changed back to investigational)
7/1/09	4/21/09	4/21/09	Addition of BSGI to policy, references added (BCBSA, TEC, articles by Zhou, Brenner.
3/1/11	1/4/11	1/4/11	Routine maintenance; no change in policy statement. Added molecular breast imaging modality to policy title.
11/1/13	8/22/13	8/27/13	Routine maintenance; policy updated to mirror BCBSA. No change to policy position.
3/1/15	12/9/14	12/29/14	Routine maintenance; updated rationale and references. New investigational policy statement for preoperative or intraoperative sentinel lymph node detection using handheld or mounted mobile gamma cameras added.
3/1/16	12/10/15	12/10/15	Routine maintenance
3/1/17	12/13/16	12/13/16	Updated rationale and references. Title changed: Scintimammography and Gamma Imaging of the Breast and Axilla. Policy status change: Localization of sentinel lymph nodes using radiopharmaceutical and gamma detection has been established for individuals who have breast cancer undergoing sentinel lymph node biopsy for detection of axillary metastases.
1/1/18	10/19/17	10/19/17	Rationale updated, references 46-47 and 49-50 updated. No change in policy status.

1/1/19	10/16/18	10/16/18	Routine policy maintenance, added reference #51. No change in policy status.
1/1/20	10/15/19		Routine policy maintenance. No change in policy status.
1/1/21	10/20/20		Rationale updated, references 40, 41 and 50 added. No change in policy status.
1/1/22	10/19/21		Routine policy update, no change in policy status.
1/1/23	10/18/22		Routine policy maintenance, reference #48 removed. No change in policy status.
1/1/24	10/17/23		Routine policy maintenance. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2024

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: 4/30/00	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: SCINTIMAMMOGRAPHY AND GAMMA IMAGING OF BREAST AND AXILLA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	See policy criteria
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A