

Medical Policy



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Title: Scintimammography and Gamma Imaging of the Breast and Axilla

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: • With dense breasts or high risk for breast cancer	Interventions of interest are: • Scintimammography, breast-specific gamma imaging, and molecular breast imaging as an adjunct to mammography	Comparators of interest are: • Mammography only • Ultrasonography • Magnetic resonance imaging	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity
Individuals: • With indeterminate or suspicious breast lesions	Interventions of interest are: • Scintimammography, breast-specific gamma imaging, and molecular breast imaging	Comparators of interest are: • Mammographic spot compression views • Ultrasonography • Magnetic resonance imaging	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With breast cancer undergoing detection of residual tumor after neoadjuvant therapy	Interventions of interest are: • Scintimammography and breast-specific gamma imaging	Comparators of interest are: • Magnetic resonance imaging • Fluorine 18 fluorodeoxyglucose positron emission tomography • Ultrasonography	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity
Individuals: • With breast cancer undergoing surgical planning for breast-conserving therapy	Interventions of interest are: • Scintimammography and breast-specific gamma imaging	Comparators of interest are: • Magnetic resonance imaging	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity
Individuals: • With breast cancer undergoing detection of axillary metastases	Interventions of interest are: • Scintimammography and breast-specific gamma imaging	Comparators of interest are: • Surgical nodal dissection	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity
Individuals: • With breast cancer undergoing sentinel lymph node biopsy for detection of axillary metastases	Interventions of interest are: • Radiopharmaceutical and gamma detection for localization of sentinel lymph nodes	Comparators of interest are: • Localization of sentinel lymph nodes without radiopharmaceutical and gamma detection	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity

DESCRIPTION

Scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) use radiotracers with nuclear medicine imaging as a diagnostic tool for abnormalities of the breast. These tests are distinguished by 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 1 or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer.

OBJECTIVE

The objective of this policy is to determine whether detection of tumors with scintimammography, breast-specific gamma imaging, molecular breast imaging, or lymphoscintigraphy improves the net health outcome in individuals at high or indeterminate risk of breast cancer.

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 (see TEC Special Report¹).

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. Special camera positioning to include the axilla may be included when the area of interest is evaluation for axillary metastases. Scintimammography using conventional imaging modalities has relatively poor sensitivity in detecting smaller lesions (eg, <15 mm), because of the relatively poor resolution of conventional gamma cameras in imaging the breast.

Breast-Specific Gamma Imaging

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 images can be compared with mammographic images. BSGI and MBI differ primarily in the number and type of detectors used (eg, multicrystal arrays of cesium iodide or sodium iodide, or nonscintillating, semiconductor materials, such as cadmium zinc telluride). In some configurations, a detector is placed on each side of the breast and used to lightly compress it. The maximum distance between the detector and the breast is therefore from the surface to the midpoint of the breast. Much research on BSGI and MBI has been conducted at the Mayo Clinic. The radiotracer typically used is technetium Tc-99m sestamibi. MBI imaging takes approximately 40 minutes.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 biopsy after radiotracer injection. Surgical removal of 1 or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer. Several trials have compared outcomes following sentinel lymph node biopsy versus axillary lymph node dissection for managing patients with breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-32 examined whether sentinel lymph node dissection (SLND) provides similar survival and regional control as full axillary lymph node dissection in the surgical staging and management of patients with clinically invasive breast cancer. This multicenter randomized controlled trial included 5611 women and observed statistically similar results for overall survival, disease-free survival, and regional control based on 8-year Kaplan-Meier estimates.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 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.⁵ However, axillary node dissection was associated with significantly greater surgical morbidity (eg, 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 Tc-99m sestamibi (marketed by Draxis Specialty Pharmaceuticals Inc., Cardinal Health 414, LLC, Mallinckrodt Inc., and Pharmalucence Inc.). The product label states that 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."⁶

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

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

The primary radiopharmaceuticals used for lymphoscintigraphy include Tc 99m pertechnetate-labeled colloids and Tc 99m tilmanocept (Lymphoseek).¹⁰ Whereas, Tc 99m sulfur colloid may be frequently used for intraoperative injection and detection of sentinel lymph nodes using hand-held gamma detection probe.

Radiation Exposure

Scintimammography, BSGI, and MBI

The radiation dose associated with BSGI is substantial for diagnostic breast imaging modalities. According to Appropriateness Criteria from 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 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 (ie, 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."

A 2010 article calculated mean glandular doses, and lifetime attributable risks (LAR) of cancer, due to film mammography, digital mammography, BSGI, and positron emission mammography (PEM).¹³ The author, a consultant to GE Healthcare and a member of the medical advisory boards of Koning (manufacturer of dedicated breast computed tomography [CT]) and Bracco (MR contrast agents), used group risk estimates from the Biological Effects of Ionizing Radiation VII report¹⁴ to assess the risk of radiation-induced cancer and mortality from breast imaging studies. For a patient with average-sized breasts (compressed thickness during mammography of 5.3 cm per breast), estimated LARs of cancer at age 40 were:

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

Corresponding LARs of cancer mortality at age 40 were:

- 1.3 per 100,000 for digital mammography (breast cancer only),
- 1.7 per 100,000 for screen film mammography (breast cancer only),
- 26 to 39 per 100,000 for BSGI, and
- 31 for 100,000 for PEM.

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

Notes: The term *molecular breast imaging* is used in different ways, sometimes for any type of breast imaging involving molecular imaging, including PEM, and sometimes it is used synonymously with the term breast-specific gamma camera, as used in this review. Use of single-photon emission computed tomography and positron emission tomography of the breast are not covered in this review.

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

REGULATORY STATUS

Several scintillation (gamma) cameras have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for “measuring and imaging the distribution of radionuclides in the human body by means of photon detection.”¹⁵ Examples of gamma cameras used in breast-specific gamma imaging are the Dilon 6800® (Dilon Technologies, Newport News, VA) and single-head configurations of Discovery NM750b (GE Healthcare, Milwaukee, WI). Dual-head cameras used in molecular breast imaging include LumaGEM™ (Gamma Medical, Salem, NH) (FDA product code IYX) and Discovery NM750b (GE Healthcare, Milwaukee, WI).

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

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

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

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.

POLICY

- A. Use of gamma detection following radiopharmaceutical administration for localization of sentinel lymph nodes in patients with breast cancer may be considered **medically necessary**.
- B. Scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) are considered **experimental / investigational** in all applications, including, but not limited to, their use as an adjunct to mammography or in staging the axillary lymph nodes.

Policy Guidelines

1. The most commonly-used radiopharmaceutical in BSGI or MBI is technetium 99m (Tc 99m) sestamibi.
2. The 2013 Breast Imaging Reporting and Data System (BI-RADS) breast assessment and breast tissue categories are in Table PG1.

Table PG1. 2013 BI-RADS Breast Assessment and Breast Tissue Categories

Grading Schema	Category
Assessment categories	
0	Incomplete
1	Negative
2	Benign
3	Probably benign
4	Suspicious
5	Highly suggestive of malignancy
6	Known biopsy-proven malignancy
Breast tissue categories	
a	Breasts are almost entirely fatty
b	Scattered areas of fibroglandular density
c	Heterogeneously dense
d	Extremely dense

BI-RADS: Breast Imaging Reporting and Data System.

Source:

<http://www.acr.org/~media/ACR/Documents/PDF/QualitySafety/Resources/BIRADS/01%20Mammography/02%20%20BIRADS%20Mammography%20Reporting.pdf>

3. The most commonly used radiopharmaceuticals for sentinel lymph node detection using either lymphoscintigraphy or hand-held gamma detection include Tc 99m-labelled colloids (eg, sulfur colloid).
4. Among the other possible radiopharmaceuticals is Lymphoseek®.

RATIONALE

This evidence review has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through July 9, 2018.

This review has been informed by a TEC Assessment (2013).¹⁶ Lymphoscintigraphy and radioactive localization for sentinel lymph node biopsy were not discussed in that TEC Assessment. The scope of this evidence review was expanded to include lymphoscintigraphy and radioactive localization for sentinel lymph node biopsy (SLNB).

A few studies have reported on the change in patient management after imaging, but there were insufficient data to determine whether these changes led to improvements in health outcomes. A subsequent TEC Special Report (2013) reviewed evidence for asymptomatic women undergoing breast cancer screening, including those with dense breasts or at high risk of breast cancer.¹ 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

The purpose of scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) is to confirm a diagnosis of breast cancer for the following populations: (1) women with dense breasts or are at high risk for breast cancer and (2) women with indeterminate breast lesions.

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?

Patients

The relevant populations of interest are:

1. Women with dense breasts or high risk for breast cancer, as part of routine screening
2. 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.

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 by indication to make decisions about:

1. Women with dense breasts or high risk for breast cancer: mammography alone, ultrasonography, or MRI
2. 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. For women already diagnosed with breast cancer, true-positives can inform surgical and other management decisions.

False-positives may lead to unnecessary biopsies in women in need of a definitive diagnosis. For women already diagnosed with breast cancer, false-positives may lead to unnecessary treatment.

True-negatives may reduce the number of biopsies in women in need of a definitive breast cancer diagnosis. For women already diagnosed with breast cancer, true-negatives can inform surgical and other management decisions.

False-negatives may prevent women from pursuing the necessary evaluations to determine a breast cancer diagnosis. For women already diagnosed with breast cancer, false-negatives may result in incorrect treatment decisions.

Timing

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 diagnosis of cancer. Longer follow-up would be necessary to determine the effects on overall survival.

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess the clinical validity of gamma imaging, studies should report sensitivity, specificity, positive (PPV) and negative (NPV) predictive values. Additionally, studies reporting false-positive rates and false-negative rates are informative.
- To assess the clinical utility of gamma imaging, studies should demonstrate how results of gamma imaging impact treatment decisions and overall management of the patient.

Dense Breasts or High Risk for Breast Cancer

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and

unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Several studies have assessed BSGI and MBI in women at high risk for breast cancer.

Prospective Studies: Rhodes et al (2015) reported on a prospective study that evaluated MBI using a lower dose of technetium Tc 99m (Tc 99m) sestamibi (dispensed activity, 300 MBq [\approx 2.4 mSv] vs 740 MBq in conventional doses).¹⁷ Like an earlier study (discussed next), participants were asymptomatic and had heterogeneously or extremely dense breasts. More than half (57%) had an additional risk factor for breast cancer, representing varying degrees of risk (eg, 10% had a personal history of breast cancer) and 22% (without a personal history of breast cancer) had elevated Gail model risk score. Of 1651 eligible women, 1585 (96%) underwent both mammography and MBI. Images were interpreted by radiologists blinded to results of the other test using a standardized lexicon, and reference standards included follow-up of both positive and negative test results for 11 months minimum. Twenty-one (1.3%) of 1583 women were diagnosed with cancer. For detection of all cancers (invasive cancers plus ductal carcinoma in situ), sensitivity was 24% (95% confidence interval [CI], 11% to 45%) for mammography and 91% (95% CI, 71% to 97%) for mammography plus MBI ($p < 0.001$); specificity was 89% (95% CI, 88% to 91%) and 83% (95% CI, 81% to 85%; $p < 0.001$); PPV was 3% (95% CI, 1% to 7%) and 7% (95% CI, 4% to 10%; $p = 0.021$); and NPV was 99% (95% CI, 98% to 99%) and 100% (95% CI, 99% to 100%; $p < 0.001$), all respectively. The addition of MBI increased the recall rate to 18% from 11% with mammography alone ($p < 0.001$), and the biopsy rate to 4% from 1% ($p < 0.001$).

Rhodes et al (2011) prospectively compared MBI (with dual-head cadmium zinc telluride detectors), mammography, and a combination of both modalities in 936 asymptomatic women with heterogeneously or extremely dense breasts on a prior mammogram, as well as additional risk factors (*BRCA* variants, a personal history of breast cancer).¹⁸ Risk levels in these different populations varied substantially. Eleven (1.2%) of 936 women were diagnosed with cancer. Overall sensitivity was 82% (95% CI, 52% to 95%) for MBI, 27% (95% CI, 10% to 57%) for mammography, and 91% (95% CI, 62% to 98%) for both combined. Specificity was 93% (95% CI, 91% to 94%) for MBI, 91% (95% CI, 89% to 93%) for mammography, and 85% (95% CI, 83% to 87%) for both (sensitivity and specificity for MBI vs mammography, both $p = 0.07$). The number of breast cancers diagnosed per number of biopsies performed was 28% for MBI and 18% for mammography.

Several studies have evaluated the diagnostic accuracy of BSGI in patients with dense breasts or high risk for breast cancer who had normal mammographic findings. Brem et al (2005) prospectively evaluated 94 women with BSGI who were considered at high risk for breast cancer despite normal mammographic findings.¹⁹ High risk was defined as a 5-year breast cancer risk of 1.66%, as determined by the Gail model. Of 94 women in the study, 35 (37%) had a history of some type of breast cancer or atypical hyperplasia. Sixteen (17%) women had abnormal BSGI findings. Follow-up ultrasounds in 11 of them identified a hypoechoic lesion that was biopsied. The 5 remaining patients had normal ultrasound results and were followed with repeat BSGI at 6

months, all of which were normal. Among the 11 women who underwent ultrasound-guided biopsy, 2 (12%) invasive cancers were identified. The sensitivity of BSGI was 100% (95% CI, 22% to 100%) and the specificity was 85%. The study was limited by the small number of cancers detected.

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

Brem et al (2016) retrospectively reviewed BSGI findings in 849 women at increased risk of breast cancer (eg, *BRCA1*, *BRCA2*, family history of breast cancer) whose mammogram findings were classified as negative, benign, or probably benign (BIRADS categories 1, 2, or 3).²¹ BSGI examinations were performed with a single-head high-resolution breast-specific gamma camera, initially at a mean of 781 MBq Tc 99m sestamibi (n=653) but the protocol was then modified to a mean of 296 MBq (n=196). A total of 212 (25%) of 849 women had a positive BSGI examination (recall rate). Fourteen (6.6%) of the 212 women who tested positive were found to have breast cancer. Eight of the 14 cancers were ductal carcinoma in situ. The incremental cancer detection rate with BSGI was 1.6% (14/849), and the invasive cancer rate was 0.7% (6/849).

Although the use of BSGI (or MBI) has been proposed for women at high risk of breast cancer, there is controversy and speculation over whether some women (eg, those with *BRCA* variants) have a heightened radiosensitivity.^{22,23} If women with *BRCA* variants are more radiosensitive than the general population, studies may underestimate the risks of breast imaging with ionizing radiation (ie, 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.

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.

No direct evidence on the clinical utility of scintimammography, BSGI, and MBI for this indication 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. Because the clinical validity of scintimammography, BSGI, and MBI has not been established, a chain of evidence supporting their clinical utility in this population cannot be constructed.

Section Summary: Dense Breasts or High Risk for Breast Cancer

Three prospective studies have compared the incremental difference in diagnostic accuracy when BSGI or MBI is added to mammography in women at increased risk, and both MBI studies were by the same research group. Sensitivity was higher with combined BSGI (or MBI) and mammography, but specificity was lower. Studies of women at increased risk of breast cancer and negative mammograms found that a small number of additional cancers were detected, but the recall rate was relatively high. Studies tended to include women at different risk levels (eg, women with dense breasts and those with *BRCA1*). Moreover, any potential benefits need to be weighed against potential risks of additional radiation exposure and risks from breast biopsy for false-negative findings. Even in studies that used a reduced dose of Tc 99m sestamibi, the effective dose (2.4 mSv) exceeded that of digital mammography (≈ 0.5 mSv) by a factor of 4.8. In addition, a large, high-quality, head-to-head comparison of BSGI (or MBI) and MRI would be needed, especially for women at high risk of breast cancer, because MRI, alternated with mammography, is currently the recommended screening technique.

Indeterminate or Suspicious Breast Lesions

Several studies have addressed the use of BSGI to diagnose breast lesions in women who have indeterminate or suspicious lesions.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Cho et al (2016) retrospectively reviewed breast lesions in 162 women diagnosed with BI-RADS category 4 lesions (suspicious) on mammography or ultrasonography.²⁴ Patients had subsequently undergone BSGI with Tc 99m sestamibi at 925 to 1110 MBq. Using biopsy-confirmed pathologic evaluation as the criterion standard, 66 (40.7%) of 162 lesions were found to be malignant. The sensitivity and specificity of BSGI were 90.9% (95% CI, 81.3% to 96.6%) and 78.1% (95% CI, 68.5% to 85.9%), respectively. The PPV was 74.1% (95% CI, 63.1% to 83.2%) and the NPV was 92.6% (95% CI, 84.6% to 97.2%). For lesions of 1 cm or smaller, the

sensitivity of BSGI was 88.0% (95% CI, 68.6% to 97.5%) and the specificity was 86.8% (95% CI, 71.9% to 95.6%). For lesions larger than 1 cm, the sensitivity was higher (92.7%; 95% CI, 80.1% to 98.5%) and the specificity was lower (61.5%; 95% CI, 44.6% to 76.6%).

Meissnitzer et al (2015) in Austria evaluated BSGI in the diagnostic workup of 67 patients with 92 suspicious breast lesions identified on mammography and/or ultrasonography.²⁵ Biopsy results were obtained as the reference standard in all patients, and 67 (73%) of 92 lesions were malignant. BSGI images were interpreted visually and semiquantitatively. Overall BSGI sensitivity and specificity were 90% and 56%, respectively, compared with ultrasound sensitivity and specificity of 99% and 20%, respectively. For lesions smaller than 1 cm, the sensitivity of BSGI was 60%.

Tan et al (2014) assessed the diagnostic accuracy of dual-phase BSGI (at 10-15 minutes and at 90-120 minutes) in 76 women at a single institution in China who had suspicious breast masses.²⁶ On pathologic review, 54 (59%) of 92 tumors were malignant, and 38 (41%) were benign. Using receiver operating characteristic–determined cut points for visual and semiquantitative interpretation, sensitivity and specificity were maximized when a combination of visual and early-phase semiquantitative interpretation was used (85% and 92%, respectively) compared with either analysis or delayed-phase semiquantitative analysis alone.

Spanu et al (2012) assessed the clinical impact of BSGI (using Tc 99m tetrofosmin) in a prospective study of 467 women who had suspicious lesions on physical examination, MRI, ultrasound, or mammogram.²⁷ Histopathology reports were obtained in all cases. BSGI results were true-positives in 408 of 420 breast cancer patients (sensitivity, 97%), including the detection of multifocal, multicentric disease and bilateral disease, and were false-negatives in 12 breast cancer patients. BSGI results were true-negatives in 40 of 47 patients with benign lesions (specificity, 85%). The authors calculated that BSGI provided additional value compared with mammography in 141 (30%) of 467 patients, 108 with breast cancer and 33 with benign lesions.

Hruska et al (2008) evaluated 150 patients with BI-RADS classification 4 or 5 lesions less than 2 centimeters identified on mammography or ultrasound who were scheduled for a biopsy. The patients underwent MBI using a dual-head, breast-specific gamma camera.²⁸ Results from 3 blinded readers were averaged. In 88 patients, 128 cancer tumors were found. The per-lesion sensitivity with the dual-head camera was 90% (115/128) for all lesions and 82% (50/61) for lesions of 1 centimeter or less. Overall, MBI specificity (across patients) was 69%. The proportion of patients with cancer in this study was higher than might have been expected in a screening population with suspicious lesions on mammography. This was the case because preference was given to those who had a high suspicion of cancer or were likely to have multifocal or multicentric disease.

Spanu et al (2008) evaluated 145 consecutive patients scheduled for biopsy with MBI (using Tc 99m tetrofosmin) of suspected breast lesions.²⁹ With an 86% prevalence of disease, the sensitivity of MBI was 98% per patient (100% for tumors >10 mm, 91% for tumors ≤10 mm). Per-lesion specificity was 86%. Four cancers were missed, three of which were detected by mammography. The authors suggested using MBI for surgical planning or avoiding biopsy, but the NPV (83%) was not high enough to forgo biopsy.

Brem et al (2007) compared BSGI with MRI in 23 women who had 33 indeterminate lesions.³⁰ Eight patients had 9 pathologically confirmed cancers. BSGI demonstrated a significantly greater specificity (71%; 95% CI, 49% to 87%) than MRI (25%; 95% CI, 11% to 47%; $p < 0.05$) and comparable sensitivity (BSGI, 89% [95% CI, 51% to 99%] vs MRI, 100% [95% CI, 63% to 100%]), PPV (BSGI, 53% [95% CI, 27% to 78%] vs MRI, 33% [95% CI, 17% to 54%]), and NPV (BSGI, 94% [95% CI, 71% to 100%] vs MRI, 100% [95% CI, 52% to 100%]). The authors noted that the 100% sensitivity and 25% specificity of MRI would likely was due to the small number of cancers in the study.

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.

No direct evidence on the clinical utility of scintimammography, BSGI, and MBI for this indication 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.

Because the clinical validity of scintimammography, BSGI, and MBI has not been established, a chain of evidence supporting their clinical utility in this population cannot be constructed.

Section Summary: Indeterminate or Suspicious Breast Lesions

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

Scintimammography and BSGI to Inform Treatment

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and

whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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

Clinical Context and Test Purpose

The purpose of scintimammography and BSGI is to inform a treatment plan for women diagnosed with breast cancer. This review evaluates the use of these procedures among the following populations: (1) women with breast cancer undergoing screening to detect residual tumor after neoadjuvant therapy, (2) women with breast cancer undergoing planning for breast-conserving surgery, and (3) women with breast cancer undergoing screening to detect axillary metastases.

The questions addressed in this evidence review are:

1. 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 screening for residual tumor after neoadjuvant therapy?
2. Does the use of scintimammography or BSGI improve the net health outcome compared with MRI in women with breast cancer undergoing planning for breast-conserving surgery?
3. 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?

Patients

The relevant populations of interest are:

1. Women with breast cancer undergoing screening to detect any residual tumor tissue following neoadjuvant therapy
2. Women with breast cancer undergoing planning for breast-conserving surgery
3. Women with breast cancer undergoing screening to detect any axillary metastases.

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:

1. Women with breast cancer undergoing screening to detect any residual tumor tissue following neoadjuvant therapy: MRI, fluorine 18 fluorodeoxyglucose positron emission tomography, or ultrasonography
2. Women with breast cancer undergoing planning for breast-conserving surgery: MRI
3. Women with breast cancer undergoing screening to detect any axillary metastases: surgical node dissection

Outcomes

True-positives can inform decisions to initiate treatment among newly diagnosed women with breast cancer. For women already diagnosed with breast cancer, true-positives can inform surgical and other management decisions.

False-positives may lead to unnecessary biopsies in women in need of a definitive diagnosis. For women already diagnosed with breast cancer, false-positives may lead to unnecessary treatment.

True-negatives may reduce the number of biopsies in women in need of a definitive breast cancer diagnosis. For women already diagnosed with breast cancer, true-negatives can inform surgical and other management decisions.

False-negatives may prevent women from pursuing the necessary evaluations to determine a breast cancer diagnosis. For women already diagnosed with breast cancer, false-negatives may result in incorrect treatment decisions.

Timing

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.

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess the clinical validity of gamma imaging, studies should report sensitivity, specificity, PPV, and NPV. Additionally, studies reporting false-positive rates and false-negative rates are informative.
- To assess the clinical utility of gamma imaging, studies should demonstrate how results of gamma imaging impacted treatment decisions and overall management of the patient.

Detection of Residual Tumor After Neoadjuvant Therapy

Systematic Reviews

A systematic review and meta-analysis by Guo et al (2016) identified 14 studies investigating the performance of BSGI with Tc 99m for evaluating the response to neoadjuvant therapy in patients with breast cancer.³¹ In all studies, histopathologic results were obtained after surgery and used as the criterion standard. Study sizes ranged from 14 to 122 patients (total N=503 patients). Most studies had fewer than 30 patients. Thirteen studies were prospective and 1 retrospective. Only 3 studies conducted BSGI both before and after treatment. The sensitivity of BSGI for identifying residual disease ranged from 33% to 100%, with a pooled sensitivity of 86% (95% CI, 78% to 92%). The specificity ranged from 17% to 95%, and the pooled specificity was 69% (95% CI, 64% to 74%).

Retrospective Studies

The largest study included in the Guo systematic review is the retrospective and single-center by Lee et al (2014).³² It evaluated BSGI detection of residual tumor after neoadjuvant chemotherapy (primarily anthracycline and taxane-based) in 122 women who had pathologically confirmed invasive breast cancer. All patients underwent BSGI and dynamic contrast-enhanced breast MRI after completing neoadjuvant therapy. Surgeons consulted BSGI and MRI for surgical planning (ie, either breast-conserving therapy [64%] or mastectomy [36%]). Of 122 patients, 104 (85%) had residual disease by pathologic review. BSGI sensitivity was 74%, specificity was 72%, NPV was 33%, and PPV was 94%. The sensitivity of BSGI varied by cellularity and size of residual tumor (greater sensitivity with greater cellularity and greater tumor size).

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

Section Summary: Detection of Residual Tumor After Neoadjuvant Therapy

A systematic review of studies evaluating BSGI for detecting residual tumor after neoadjuvant therapy found a pooled sensitivity of 86% and a pooled specificity of 69%, compared with histopathologic analysis. No studies were identified that compared the diagnostic accuracy of BSGI with other imaging approaches, or that investigated the impact of BSGI on patient management decisions or health outcomes.

Surgical Planning for Breast-Conserving Therapy

Edwards et al (2013) retrospectively assessed changes in the surgical management of 218 women who had breast cancer and were eligible for breast-conserving therapy.³³ All patients had undergone preoperative BSGI or MRI. Twelve percent of patients who had BSGI and 29% of those who had MRI changed to mastectomy. On pathologic review, no patient who underwent a mastectomy was eligible for breast-conserving therapy. Of patients who received breast-conserving therapy, 15% of those who had BSGI and 19% of those who had MRI required a single re-excision because of positive surgical margins, and 14% and 6%, respectively, required mastectomy. Based on this retrospective study, the clinical utility of BSGI for guiding surgical decision making in breast cancer patients would appear limited.

Section Summary: Surgical Planning for Breast-Conserving Therapy

One retrospective study is insufficient to determine the clinical utility of BSGI for guiding surgical decision making in breast cancer patients. In this study, results suggested that MRI identified

more patients than BSGI who were not appropriate candidates for breast-conserving therapy. Prospective comparative studies are needed.

Detection of Axillary Metastases

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.³⁴ In a review of studies published between 1994 and 1998, Taillefer (1999) showed a sensitivity of 77% and a specificity of 89%.³⁵

Case Series

Several case series using different radiopharmaceuticals have shown sensitivities in the high 80% to 90% range.^{36,37}

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 diagnostic accuracy of BSGI as reported in the available literature is not high enough for this technology to replace the current standard practice (surgical nodal dissection). 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.

Radiopharmaceutical and Gamma Detection to Inform Treatment

Clinical Context and Test Purpose

The purpose of radiopharmaceutical and gamma detection is to inform a treatment plan for women with breast cancer undergoing sentinel lymph node biopsy (SLNB) to detect axillary metastases.

The questions addressed in this evidence review are: 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?

Patients

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

Interventions

The therapy being considered is lymphoscintigraphy and radioactive localization for SLNB.

Lymphoscintigraphy and radioactive localization are techniques that map sentinel nodes by identifying the lymph drainage basin, determining the number of sentinel nodes, differentiating the sentinel nodes, and marking the sentinel node over the skin for a biopsy.

Comparators

The following practice is currently being used to make decisions about detecting axillary metastases: localization without radiopharmaceuticals or gamma detection.

Outcomes

True-positives can inform decisions to initiate treatment among newly diagnosed women with breast cancer. For women already diagnosed with breast cancer, true-positives can inform surgical and other management decisions.

False-positives may lead to unnecessary biopsies in women in need of a definitive diagnosis. For women already diagnosed with breast cancer, false-positives may lead to unnecessary treatment.

True-negatives may reduce the number of biopsies in women in need of a definitive breast cancer diagnosis. For women already diagnosed with breast cancer, true-negatives can inform surgical and other management decisions.

False-negatives may prevent women from pursuing the necessary evaluations to determine a breast cancer diagnosis. For women already diagnosed with breast cancer, false-negatives may result in incorrect treatment decisions.

Timing

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.

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess the clinical validity of gamma imaging, studies should report sensitivity, specificity, PPV, and NPV. Additionally, studies reporting false-positive rates and false-negative rates are informative.
- To assess the clinical utility of gamma imaging, studies should demonstrate how results of gamma imaging impact treatment decisions and overall management of the patient.

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).³⁸ This analysis examined the false-negative rate of SLNB in patients with breast cancer by localization technique: radioactive tracer alone, dye alone, or combination of radioactive tracer and dye. The false-negative rate was highest for the dye-only group at 8.6% (95% CI, 6.7% to 10.8%) while the tracer-only group had a false-negative rate of 7.4% (95% CI, 5.6% to 9.3%), and the combination of dye-and-tracer had the lowest false-negative rate at 5.9% (95% CI, 4.8% to 7.1%). The Q statistic for heterogeneity indicated that the 3 groups were not all equal ($p=0.050$). Subsequent pairwise comparisons revealed a difference between the dye-only and the dye-and-tracer categories ($p=0.018$), but no significant difference was seen between tracer-only and dye-only ($p=0.370$) or between tracer-only and dye-and-tracer ($p=0.178$).

Randomized Controlled Trials

A randomized study by van der Vorst et al (2012) compared Tc 99m radiotracer plus near-infrared fluorescence imaging using indocyanine green with or without the use of a patent blue dye for localization of sentinel lymph nodes.³⁹ Twenty-four consecutive breast cancer patients who were all undergoing SLNB were studied. Of the 23 cases with successful sentinel lymph node mapping, the lymph nodes were both radioactive and fluorescent in 100% of cases, whereas only 84% of the lymph nodes showed blue dye staining. In addition, for 25% of cases, the gamma probe was needed to identify and locate the sentinel nodes during the first 15 minutes of localization.

Nonrandomized Trials

Johnson et al (2011) conducted a single institution study assessing 699 patients with operable breast cancer for SLNB.⁴⁰ Using intraoperative Tc 99m–labeled radiopharmaceutical tracer subareolar injection, the sentinel node was localized in 98.6% of cases.

Martin et al (2000) reported a prospective multi-institutional study examining 758 patients who were clinical stage T1-2, N0, M0 invasive breast cancer and who received radioactive colloid and isosulfan blue dye injections before axillary SLNB.⁴¹ 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.⁴²⁻⁴⁴ Note that lymphoscintigraphy uses planar or tomographic imaging that differs from the use of hand-held gamma detection probe of radioactive nodes during surgery.

Section Summary: Radiopharmaceutical and Gamma Detection to Inform Treatment

For individuals who have breast cancer, are undergoing SLNB to detect any axillary metastases, and who have received radiopharmaceutical and gamma detection for localization of sentinel lymph nodes, the evidence includes 3 studies and a meta-analysis. These studies provide consistent evidence that diagnostic performance using radiopharmaceutical and gamma detection yields high success rates in identifying sentinel lymph nodes; further, these studies would suggest that diagnostic performance trends toward better detection rates using radiopharmaceutical (as opposed to alternative methods using only blue dye). Clinical utility is demonstrated for this indication when the high diagnostic yield of sentinel lymph nodes using radiopharmaceutical and gamma detection is considered together with the evidence that SLNB provides similar long-term outcomes as full axillary lymph node dissection for control of breast cancer and offers more favorable early results with reduced arm swelling and postsurgical morbidity.

SUMMARY OF EVIDENCE

Scintimammography, BSGI, and MBI 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 (eg, women with dense breasts and those with *BRCA1*). Moreover, any potential benefits need to be weighed against the potential risks of additional radiation exposure. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

Scintimammography and BSGI for Treatment

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 with histopathologic analysis. No studies were identified that compared the diagnostic accuracy of BSGI with other imaging approaches, or that investigated the clinical utility of this potential application of BSGI. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have breast cancer undergoing surgical planning for breast-conserving therapy who receive scintimammography and BSGI, 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, results suggested that magnetic resonance imaging identified more patients than BSGI who were not appropriate candidates for breast-conserving therapy. Prospective comparative studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 validity, and treatment-related morbidity. A meta-analysis of the available diagnostic accuracy studies found that the sensitivity and specificity of BSGI are not high enough for this technology to replace the current standard practice, surgical nodal dissection. The evidence is insufficient to determine the effects of the technology on health outcomes.

Radiopharmaceutical and Gamma Detection for Treatment

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

Society of Nuclear Medicine

The Society of Nuclear Medicine released a 2010 procedure guideline on breast scintigraphy using breast-specific gamma cameras.⁴⁵ The guideline is based on consensus, and most of it is devoted to procedures and specifications of the examination, documentation and recording, quality control, and radiation safety. The guidelines also listed common clinical indications for breast-specific gamma imaging but did not discuss the level of evidence for each indication.

American College of Obstetricians and Gynecologists

In 2017 the American College of Obstetricians and Gynecologists updated its 2011 practice bulletin on breast cancer screening.⁴⁶ There is no discussion or recommendation for scintimammography for routine screening in the 2017 practice bulletin.

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 2016),¹¹ palpable breast masses (last reviewed in 2017),⁴⁷ and workup of breast pain (last reviewed in 2016).⁴⁸ New guidelines on screening for breast cancer in above average risk patients (last reviewed in 2017) do not mention breast-specific gamma imaging.⁴⁹

American Society of Clinical Oncology

The American Society of Clinical Oncology (2016) reaffirmed its 2014 recommendations on the use of sentinel node biopsy for patients with early-stage breast cancer.⁵⁰ 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 [sentinel node

biopsy]. Women who have large or locally advanced invasive breast cancer (tumor size T3/T4), inflammatory breast cancer, or ductal carcinoma in situ (when breast-conserving surgery is planned) or are pregnant should not undergo SNB.”

National Comprehensive Cancer Network

The National Comprehensive Cancer Network’s guidelines (v.1.2018) an invasive breast cancer with clinical stage I, IIA, IIB, and IIIA T3, N1, M0 (BINV-D) include sentinel node mapping and excision for clinically node-negative patients at time of diagnosis or following negative fine-needle aspiration or core biopsy of clinically positive nodes at time of diagnosis.⁵¹ If the sentinel nodes are found to be negative on pathologic examination, then no further axillary surgery is suggested (category 1 recommendation).

Network guidelines on breast cancer screening and diagnosis (v.2.2018) state: “Current evidence does not support the routine use of molecular imaging (e.g. breast-specific gamma imaging, sestamibi scan, or positron emission mammography) as screening procedures, but there is emerging evidence that these tests may improve detection of early breast cancers among women with mammographically dense breasts. However, the whole-body effective radiation dose with these tests is between 20-30 times higher than that of mammography.”⁵²

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might impact this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02324387	Tc99m Sestamibi Molecular Breast Imaging	100	Jun 2019
NCT02556684	Breast-Specific Gamma Imaging and Locally Advanced Breast Cancer Undergoing Neoadjuvant Chemotherapy (BSGILAB)	200	Oct 2020
NCT03082456	Molecular Breast Imaging in Screening Breast Cancer	1800	Jun 2018 (ongoing)
NCT02744053	Multimodality Breast Imaging for the Assessment of Tumor Response to Neoadjuvant Chemotherapy in Triple Negative Breast Cancer Patients	100	Nov 2020

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

78195 Lymphatics and lymph nodes 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)
- A4641 Radiopharmaceutical, diagnostic, not otherwise classified
- A9500 Technetium tc-99m sestamibi, diagnostic, per study dose
- A9502 Technetium Tc-99m tetrofosmin, diagnostic, per study dose
- A9520 Technetium tc-99m, tilmanocept, diagnostic, up to 0.5 millicuries
- A9541 Technetium Tc-99m sulfur colloid, diagnostic, per study dose, up to 20 millicuries
- S8080 Scintimammography (radioimmunosintigraphy of the breast), unilateral, including supply of radiopharmaceutical

ICD-10 Diagnoses

- C50.011 Malignant neoplasm of nipple and areola, right female breast
- C50.012 Malignant neoplasm of nipple and areola, left female breast
- C50.021 Malignant neoplasm of nipple and areola, right male breast
- C50.022 Malignant neoplasm of nipple and areola, left male breast
- C50.111 Malignant neoplasm of central portion of right female breast
- C50.121 Malignant neoplasm of central portion of right male breast
- C50.122 Malignant neoplasm of central portion of left male breast
- C50.211 Malignant neoplasm of upper-inner quadrant of right female breast
- C50.212 Malignant neoplasm of upper-inner quadrant of left female breast
- C50.221 Malignant neoplasm of upper-inner quadrant of right male breast
- C50.222 Malignant neoplasm of upper-inner quadrant of left male breast
- C50.311 Malignant neoplasm of lower-inner quadrant of right female breast
- C50.312 Malignant neoplasm of lower-inner quadrant of left female breast
- C50.321 Malignant neoplasm of lower-inner quadrant of right male breast
- C50.322 Malignant neoplasm of lower-inner quadrant of left male breast
- C50.411 Malignant neoplasm of upper-outer quadrant of right female breast
- C50.412 Malignant neoplasm of upper-outer quadrant of left female breast
- C50.421 Malignant neoplasm of upper-outer quadrant of right male breast
- C50.422 Malignant neoplasm of upper-outer quadrant of left male breast
- C50.511 Malignant neoplasm of lower-outer quadrant of right female breast
- C50.512 Malignant neoplasm of lower-outer quadrant of left female breast
- C50.521 Malignant neoplasm of lower-outer quadrant of right male breast
- C50.522 Malignant neoplasm of lower-outer quadrant of left male breast
- C50.611 Malignant neoplasm of axillary tail of right female breast
- C50.612 Malignant neoplasm of axillary tail of left female breast
- C50.621 Malignant neoplasm of axillary tail of right male breast
- C50.622 Malignant neoplasm of axillary tail of left male breast
- C50.811 Malignant neoplasm of overlapping sites of right female breast
- C50.812 Malignant neoplasm of overlapping sites of left female breast
- C50.821 Malignant neoplasm of overlapping sites of right male breast
- C50.822 Malignant neoplasm of overlapping sites of left male breast

REVISIONS

01-28-2011	Policy added to the bcbsks.com web site.
09-17-2013	Updated Description section.
	Updated Rational section.
	Updated Reference section.
03-31-2015	Policy title changed from "Scintimammography/Breast Specific Gamma Imaging/Molecular Breast Imaging".
	Updated Description section.
	In Policy section: ▪ Added Policy Guidelines.
	Updated Rationale section.
	Updated References section.
07-08-2015	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-26-2016	Updated Description section.
	In the Policy section: ▪ Added Item A, "Use of gamma detection following radiopharmaceutical administration for localization of sentinel lymph nodes in patients with breast cancer may be considered medically necessary." ▪ In Policy Guidelines, added Items 2, 3, and 4.
	Updated Rationale section.
	In Coding section: ▪ Added CPT/HCPCS codes: 78195, A9520, A9541. ▪ Added ICD-10 codes.
	Updated References section.
10-25-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
11-07-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Removed HCPCS codes: A4642, A9568, A9572.
	Updated References section.

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