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Scintimammography and Gamma Imaging of the Breast and Axilla

Policy # 00438

Original Effective Date: 09/17/2014

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) in all applications, including but not limited to their use as an adjunct to mammography or in staging the axillary lymph nodes to be **investigational**.*

Based on review of available data, the Company considers preoperative or intraoperative sentinel lymph node detection using handheld or mounted mobile gamma cameras to be **investigational**.*

Background/Overview

Scintimammography refers to the use of radiotracers with nuclear medicine imaging as a diagnostic tool for abnormalities of the breast. BSGI, or MBI, refers to specific types of imaging machines that are used in conjunction with scintimammography to improve diagnostic performance.

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 (eg, <15 mm), because of the relatively poor resolution of conventional gamma cameras in imaging the breast. BSGI and MBI were developed to address this issue. Breast-specific gamma cameras acquire images while the patient is seated in a position similar to that in mammography, and the breast is lightly compressed. The detector head(s) is 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. BSGI and MBI have been suggested for a variety of applications. In a 2010 practice guideline for breast scintigraphy with breast specific gamma cameras, the Society of Nuclear Medicine provided a list of common uses, as follows:

1. Among patients with recently detected breast malignancy: for initial staging; detecting multicentric, multifocal, or bilateral disease; and assessing response to neoadjuvant chemotherapy.
2. Among patients at high risk for malignancy: to evaluate suspected recurrence; when mammography is limited; or when previous malignancy was occult on mammogram.

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3. Among patients with indeterminate breast abnormalities and remaining diagnostic concerns: to evaluate lesions identified by other breast imaging techniques, palpable or nonpalpable; to aid in biopsy targeting, and other settings (eg, diffuse or multiple clusters of microcalcifications, unexplained architectural distortion)
4. Among patients with technically difficult breast imaging, such as radiodense breast tissue or implants, free silicone, or paraffin injections.
5. Among patients for whom breast magnetic resonance imaging (MRI) is indicated but contraindicated, eg, patients with implanted pacemakers or pumps, or as an alternative for patients who meet MRI screening criteria, such as presence of *BRCA1/BRCA2* mutations.
6. Among patients undergoing preoperative chemotherapy: to monitor tumor response to determine the impact of therapy or plan for residual disease.

The guideline acknowledged other efforts, such as the American College of Radiology's Appropriateness Criteria and the American College of Surgeons' Consensus Conference III.

Radiopharmaceuticals

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."

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

Gamma Cameras

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." 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 Medica™ Instruments, Northridge, CA) ‡.

Radiation Exposure

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

According to another study, the radiation dose to the breast from the 20 mCi (740 MBq) dose of technetium Tc-99m sestamibi used for BSGI at 1 center is 0.13 rad or 1.3 mGy, less than the 0.75 rad the authors reported for mammography, except that the dose is given to the entire body. The authors asserted that this



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dose poses an “extremely low risk of harmful effects to the patient” but that it should be reduced by a factor of 5 to 10 if BSGI were to be used as a regular screening technique. The authors also estimated that the cost of BSGI is 3 to 4 times that of mammography.

Another article published online in August 2010 calculated mean glandular doses, and from those, lifetime attributable risks (LAR) of cancer, due to film mammography, digital mammography, BSGI, and positron emission mammography (PEM). The author, 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 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),
- 55-82 per 100,000 for BSGI (depending on the dose of technetium Tc-99m sestamibi), and
- 75 for 100,000 for PEM.

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

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

A major difference in the impact of radiation between mammography, on the one hand, and BSGI or PEM, on the other, is that for mammography, the substantial radiation dose is limited to the breast. With BSGI and PEM, all organs are irradiated, increasing the risks associated with BSGI and PEM. Researchers at the Mayo Clinic have investigated lower dose versions of MBI, and 2 small studies (NCT01653964, NCT01285440; total N=232) are ongoing. (A larger study of reduced-dose MBI in 2000 women with dense breast tissue on mammography and increased cancer risk has been suspended [NCT01723124]). Mayo Clinic researchers assert that this new approach will “make MBI comparable with screening mammography in terms of radiation exposure.” It is unclear whether this statement refers to breast exposure or whole body 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 limited to imaging with a type of breast-specific gamma camera, as used in this report.

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

Rationale/Source

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 particularly an issue for women at high risk



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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, such as scintimammography or MRI, 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 mammogram has been suggested, but the best approach is subject to debate (see TEC Special Report: Screening Asymptomatic Women with Dense Breasts and Normal Mammograms for Breast Cancer).

The TEC Assessment reviewed evidence for women undergoing breast cancer screening, including those with dense breasts or at high risk of breast cancer, and in women who had suspicious physical or imaging findings. Retrospective studies included women with a mix of indications. For all other indications, evidence was insufficient. 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 (e.g.).

BSGI for Women with Breast Cancer Risk Factors and/or Normal Mammograms

An early step in evaluating a new imaging modality for patients who may have breast cancer is to determine whether the modality can detect breast cancer or related diagnoses in women known to have the disease. However, studies of diagnostic performance in this population may be affected by disease spectrum (spectrum effect), among other possible issues. Showing that the modality can detect breast cancer, particularly smaller lesions and types that are more difficult to detect, is important, but not sufficient to demonstrate the true diagnostic performance of a test, which may vary with tumor size and characteristics, etc. Available studies are limited by the retrospective nature of most; by small sample sizes; and by patient populations with mixed indications for imaging (e.g.).

Several prospective studies assessed BSGI in women at high risk for breast cancer and/or with normal mammograms. Rhodes et al (2011) compared BSGI, mammography, and the combination of the 2 modalities in 936 asymptomatic women with heterogeneously or extremely dense breasts on prior mammogram, as well as additional risk factors. Eleven (1.2%) of 936 women had cancer. The sample included women with dense breasts and other cancer risk factors, including women with *BRCA* mutations and women with a personal history of breast cancer. Risk in these different populations varies substantially. Overall sensitivity was 82% (95% confidence interval [CI], 52 to 95) for BSGI, 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 BSGI, 91% (95% CI, 89 to 93) for mammography, and 85% (95% CI, 83 to 87) for both (sensitivity and specificity for BSGI vs mammography, both $p=0.07$). The number of breast cancers diagnosed per number of biopsies performed was 28% for BSGI and 18% for mammography.

Brem et al (2005) used a breast-specific gamma camera to evaluate 94 women considered at high risk of breast cancer, despite normal mammographic findings. 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 prior history of some



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type of breast cancer or atypical hyperplasia. Sixteen women (17%) had abnormal scintimammograms. Follow-up ultrasound in 11 of these identified a hypoechoic lesion that was biopsied. The 5 remaining patients had normal ultrasound results and were followed up with a repeat scintimammogram at 6 months, which was normal in all 5. Among the 11 women who underwent ultrasound-guided biopsy, 2 invasive cancers (12%) were identified. Sensitivity of BSGI was 100% (95% CI, 22 to 100), and specificity was 85%. The study was limited by the small number of cancers detected.

In a retrospective study of 341 women with biopsy-proven breast cancer, Rechtman et al (2014) determined the sensitivity of BSGI in dense versus nondense breasts. Mean patient age was 55 years (range, 28-89). All patients underwent preoperative BSGI and mammography; women with Breast Imaging Reporting and Data System (BI-RADS) density 1 or 2 were classified as having nondense breasts, and those with BI-RADS density 3 or 4 were classified as having dense breasts. Of 347 biopsy-proven breast cancers, BSGI was positive in 331 (overall sensitivity, 95%). In women with dense versus nondense breasts, BSGI sensitivity for detection of mammographically occult breast cancer did not differ statistically (97% vs 95%, respectively; c^2 , $p=0.102$).

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, such as those with *BRCA* mutations, have a heightened radiosensitivity. If women with *BRCA* mutations are more radiosensitive than the general population, the studies previously cited (see Background) may underestimate the risks of breast imaging with ionizing radiation (ie, mammography, BSGI, MBI, positron emission mammography (PEM), single positron emission computed tomography/computed tomography (SPECT/CT), breast-specific CT, and tomosynthesis) in these women. In contrast, ultrasound and MRI do not involve the use of radiation. More research will be 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.

Section Summary

There is scant evidence on the use of BSGI for screening women at elevated risk of breast cancer or in women with factors that limit the sensitivity of mammography. Furthermore, the relatively high radiation dose currently associated with BSGI has prompted the American College of Radiology to recommend against the use of BSGI for screening. Therefore, consideration of the potential use of BSGI for screening women with dense breasts or at high risk of breast cancer should await the development of a lower-dose regimen, and if warranted, larger, higher quality studies with study populations representative of patients encountered in clinical practice. In addition, a large, high-quality head-to-head comparison of BSGI 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.

BSGI for Women with Indeterminate or Suspicious Lesions

Several prospective studies have addressed BSGI in women who have indeterminate or suspicious lesions. Spanu et al (2012) assessed the clinical impact of BSGI in a prospective study of 467 women who had suspicious lesions on physical examination, MRI, ultrasound, or mammogram. Histopathology reports were obtained in all cases. BSGI results were true positive in 408/420 breast cancer patients (sensitivity, 97%),



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including the detection of multifocal, multicentric disease and bilateral disease, and were false negative in 12 breast cancer patients. BSGI results were true negative in 40/47 patients with benign lesions (specificity, 85%). The authors calculated that BSGI provided additional value compared with mammography in 141 (30%) of 467 patients: 108 who had breast cancer and 33 with benign lesions.

Another study by Spanu et al (2009) evaluated BSGI compared with (SPECT in 157 women with suspicious breast lesions at clinical examination and/or mammography or ultrasound. Histopathologic reports were obtained in all cases. Outcomes were calculated on a per lesion basis. Sensitivity was significantly higher for BSGI compared with SPECT (96% vs 91%, $p < 0.01$), as was diagnostic accuracy (94% vs 90%, $p < 0.01$). Specificity was identical for both imaging modalities (88%). In a similar 2007 study by Spanu et al, BSGI performance was compared with SPECT in 85 patients scheduled to undergo biopsies. Histopathologic findings were obtained in all cases. On a per lesion basis (90 malignant, 12 benign), BSGI sensitivity (97%) and accuracy (96%) were higher compared with SPECT (92% and 92%, respectively), but the differences were not statistically different. Specificity was 92% for both imaging modalities.

In a 2008 study by Hruska et al, 150 patients with BI-RADS classification 4 or 5 lesions smaller than 2 cm identified on mammography or ultrasound who were scheduled for biopsy underwent scintimammography using a dual-head, breast-specific gamma camera. Results from 3 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 a high suspicion of cancer or were likely to have multifocal or multicentric disease.

Spanu et al (2008) evaluated 145 consecutive patients scheduled for breast biopsy. With an 86% prevalence of disease, sensitivity of BSGI was 98% per patient (100% for tumors > 10 mm, 91% for tumors ≤ 10 mm). Per-lesion specificity was 86%. Four cancers were missed, 3 of which were detected by mammography. The authors suggested using BSGI for surgical planning or to avoid biopsy, but the 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. 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]), positive predictive value (PPV; BSGI, 53% [95% CI, 27 to 78] vs MRI, 33% [95% CI, 17 to 54]), and NPV (BSGI, 94% [95% CI, 71 to 100] vs MRI, 100% [95% CI, 52 to 100]). The authors noted that the 100% sensitivity and 25% specificity of MRI likely was due to the small number of cancers in the study.

In 2014, Tan et al 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. 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



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was used (85% and 92%, respectively), compared with either analysis or delayed phase semiquantitative analysis alone.

Section Summary

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. 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 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 according to the type of mammographic abnormalities included in the studies.

Ductal Carcinoma In Situ (DCIS)

Kim et al (2013) compared BSGI with dynamic contrast-enhanced MRI in 35 women who had pathologically diagnosed DCIS. Mean patient age was 48 years (range, 26-69). All patients underwent both BSGI and MRI. Overall sensitivity of BSGI and MRI were 69% and 91%, respectively. In 18 women who had microcalcifications on mammography, sensitivity of BSGI and MRI were 83% and 94%, respectively. In 17 women who had no microcalcifications on mammography, sensitivity of BSGI and MRI were 53% and 88%, respectively.

Women with Breast Cancer

Detection of Axillary Metastases

Regarding the use of scintimammography to detect axillary metastases, a review of studies published between 1994 and 1998 showed a sensitivity of 77% and specificity of 89%. More recent studies using different radiopharmaceuticals have shown sensitivities in the high 80% to 90% range. A 2011 meta-analysis reviewed 45 studies of scintimammography and also reported sensitivities and specificities in this range, with summary estimates for sensitivity of 83% (95% CI, 82 to 84) and for specificity of 85% (95% CI, 83 to 86). The test still is not accurate enough to replace surgical nodal dissection. No studies have examined patient outcomes comparing the strategy of using scintimammography to aid in decision making regarding nodal dissection versus proceeding directly to nodal dissection.

Bricou et al (2013) reviewed studies of recently-developed mobile gamma cameras for use during breast cancer surgery and/or sentinel lymph node (SLN) biopsy. In this procedure, lymphatic drainage of radioactive colloid injected preoperatively in or around the tumor site is imaged. The review included clinical studies published between January 2000 and March 2012. Thirteen studies of 8 different gamma cameras, both hand-held and arm-mounted, were identified. For preoperative SLN detection, 3 studies (total N=245) reported the comparative accuracy compared with standard lymphoscintigraphy. One study (n=88) reported a sensitivity of mobile gamma cameras that was worse than standard lymphoscintigraphy, study (n=19) reported a better sensitivity, and the third study (n=138) reported noninferiority to standard lymphoscintigraphy. A potential bias in one study was performance of gamma imaging after



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lymphoscintigraphy, permitting longer migration of the radiotracer. For intraoperative SLN detection, 7 studies (total N=264) also reported mixed results.

Detection of Residual Tumor After Neoadjuvant Therapy

In a single-center, retrospective study, Lee et al (2014) evaluated BSGI detection of residual tumor after neoadjuvant chemotherapy (primarily anthracycline and taxane-based) in 122 women who had pathologically-confirmed invasive breast cancer. Mean patient age was 46 years (range 29-71). 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%. Sensitivity of BSGI varied with cellularity and size of residual tumor (greater sensitivity with greater cellularity and greater size).

Surgical Planning for Breast-Conserving Therapy

Edwards et al (2013) retrospectively assessed changes in surgical management of 218 women who had breast cancer and were eligible for breast-conserving therapy. 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

For detection of axillary metastases, accuracy of scintimammography is insufficient to preclude nodal dissection. Clinical utility studies of scintimammography to guide decision making in this setting are lacking. Mobile gamma cameras for preoperative or intraoperative sentinel lymph node detection are in development. Current evidence comprises small studies with inconsistent results; improved sentinel lymph node detection in comparison with standard gamma probes has not been consistently shown.

Based on single retrospective studies, clinical utility of BSGI for detecting residual tumor after neoadjuvant chemotherapy or for guiding surgical decision making in breast cancer patients appears limited.

Retrospective Studies of BSGI for Women with a Mixed Set of Indications

Several retrospective studies have examined BSGI in women with mixed indications. Brem et al (2008) examined BSGI in a retrospective study of 146 consecutive patients who had a mixed set of indications, including palpable lesions with no mammographic correlation, diagnosis of multicentricity or multifocality in women with known breast cancer, and screening for women at high risk of breast cancer. The analysis was performed per lesion (n=167), not per patient. Eighty-three lesions were malignant (50%). Overall sensitivity of BSGI was 96% (95% CI, 92 to 99), and specificity was 60% (95% CI, 49 to 70). PPV was 69% (95% CI, 60 to 78), and NPV was 94% (95% CI, 88 to 99). The performance of BSGI in particular for detecting smaller tumors requires further investigation. As the authors noted, additional larger studies are needed to confirm or modify these findings.



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Park et al (2013) compared BSGI performed shortly after injection of the radiotracer with dual-phase imaging, in which BSGI was repeated 1 hour after the injection. The assumption was that technetium Tc-99m sestamibi uptake might persist on delayed images for malignant lesions, but for benign conditions it would not, thereby reducing false positive results. The study sample comprised 76 women (mean age, 49 years, range 33-61) undergoing evaluation for a palpable lesion or for a diagnosis of multicentricity and/or multifocality in women with biopsy-proven breast cancer, women being screened for breast cancer, or women with multiple lesions detected by mammography or ultrasound in which BSGI was used to determine an appropriate biopsy site. Thirteen women had breast cancer. Comparing single-phase and dual-phase BSGI, sensitivity was 77% and 69%, respectively ($p=1.0$); specificity was 83% and 95%, respectively ($p=0.008$). Thus, dual-phase imaging appeared to increase specificity without a significant effect on sensitivity. However, as the authors noted, the sample size was small. In a subsequent retrospective study by Park et al (2014), diagnostic accuracy of BSGI was increased when both visual and semiquantitative readings (normalized for tracer uptake in the unaffected contralateral breast [background uptake]) were employed compared with visual analysis alone.

Weigert et al (2012) reported data from a retrospective multicenter patient registry. This study analyzed 1042 patients drawn from 2004 patients in the registry. Women included in the study had BSGI imaging, pathologic diagnosis by biopsy, and at least 6 months of follow-up. BSGI had been recommended for patients with at least 2 of the following indications: equivocal or negative mammogram/ultrasound and an unresolved clinical concern; personal history of breast cancer or current cancer diagnosis; palpable masses negative on mammogram or ultrasound; radiodense breast tissue; or high risk for breast cancer. In this population, BSGI had a reported sensitivity of 91%, specificity of 77%, PPV of 57%, and NPV of 96%. In 139 patients who had a suspicious lesion on mammography, BSGI imaging was negative in 21 cases, 13 of which were true negatives and 8 of which were false negatives.

Section Summary

The mix of indications in these studies makes it difficult to generalize the results or to determine whether the performance of BSGI varies by indication. Also, test accuracy may vary by indication and intended use. For example, high sensitivity is important if the objective is to identify multifocal or multicentric disease; high NPV is desirable if the goal is to reduce the number of women referred for biopsy.

Meta-Analysis of BSGI

Sun et al (2013) performed a systematic review and meta-analysis on the “clinical usefulness of [BSGI] as an adjunct modality to mammography for diagnosis of breast cancer.” The authors included 19 studies in 5 separate analyses. Some of these studies were included in the evidence tables of the TEC Assessment, but others did not meet our inclusion criteria, e.g., the study population comprised women with breast cancer. Random effects models were used when there was substantial heterogeneity.

The first analysis assessed the diagnostic performance of BSGI based on 8 studies. Heterogeneity was substantial ($I^2=53\%$ for sensitivity, $I^2=91\%$ for specificity). Pooled sensitivity was 95% (95% CI, 93 to 96), and pooled specificity was 80% (95% CI, 78 to 82). Studies with different indications for BSGI were pooled, and therefore results for test accuracy are difficult to interpret. Also, to assess quality of included studies,



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the authors used a modified QUADAS instrument, which was subsequently revised by the developers. Overall, quality ratings were more favorable (i.e., higher quality) than those in the TEC Assessment.

No studies that addressed health outcomes of interest were identified, nor is there sufficient indirect evidence to infer that the use of BSGI would yield improvements in health outcomes.

Summary

Evidence to date does not provide sufficient support for any of the uses discussed. The published literature on BSGI, MBI, and scintimammography with breast specific gamma camera is limited by a number of factors. Studies include populations that usually do not represent those encountered in clinical practice and that have mixed indications. There are methodologic limitations of the available studies, which have been judged to have medium to high risk of bias, and they do not provide information about impacts on therapeutic efficacy. Limited evidence on diagnostic accuracy of BSGI indicates that the test has a relatively high sensitivity and specificity for detecting malignancy. However, evidence does not establish that BSGI improves outcomes when used as an adjunct to mammography for breast cancer screening. In available studies, Negative predictive value of BSGI has not been high enough to preclude biopsy in patients with inconclusive mammograms. The relatively high radiation dose also should be taken into account. In addition, evidence is insufficient to conclude that BSGI is better than magnetic resonance imaging for this purpose. Larger, higher-quality studies are required to determine whether BSGI has a useful role as an adjunct to mammography. For these reasons, BSGI is considered investigational.

Diagnostic accuracy of scintimammography for detecting axillary metastases is inadequate to preclude nodal dissection. Similarly, mobile gamma cameras for preoperative or intraoperative detection of sentinel lymph nodes have not shown improved diagnostic performance in comparison with standard gamma probes. Evidence comprises small studies with inconsistent results. For these reasons, detection of axillary metastases using scintimammography, BSGI, MBI, or preoperative or intraoperative mobile gamma cameras is considered investigational.

Clinical Trials

According to online site ClinicalTrials.gov, approximately 40 studies of BSGI, MBI, or portable gamma cameras are currently in progress, and many of them are being conducted at the Mayo Clinic. Active studies include:

- MBI for patients with suspected DCIS (NCT00890994); N=200; estimated completion date of December 2015.
- Low-dose Molecular Breast Imaging: Comparison of Breast Cancer Detection Rate at Initial Screening and Two-year Follow-up (NCT01723124); N=2000; estimated completion date of July 2016.
- Use of Low-dose Molecular Breast Imaging for the Detection of Small Breast Lesions (Lowdoseprebx) (NCT01285440); N=150; estimated completion date of January 2014.
- The Assessment of Molecular Breast Imaging (MBI) in Distinguishing Benign from Malignant Breast Disease (NCT01687790); N=60; estimated completion date of September 2014.
- Intraoperative Gamma Camera for Breast Cancer Surgery (NCT00757302); N=110; estimated completion date of September 2014.

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Scintimammography and Gamma Imaging of the Breast and Axilla

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- Internal Mammary Sentinel Lymph Node Biopsy in Early Breast Cancer Patients with Clinically Axillary Node–Negative (NCT01642511); N=4; estimated completion date of December 2013 (passed).

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HCPCS	A4641, A4642, A9500, A9502, A9568, A9572, S8080
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	92.19

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 09/17/2014 Medical Policy Implementation Committee approval. New policy.
 Next Scheduled Review Date: 09/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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