Scintimammography and Gamma Imaging of the Breast and Axilla

Policy # 00438
Original Effective Date: 09/17/2014
Current Effective Date: 12/14/2020

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.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider use of gamma detection following radiopharmaceutical administration for localization of sentinel lymph nodes in patients with breast cancer to be **eligible for coverage.****

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.***

Policy Guidelines

The most commonly used radiopharmaceutical in breast-specific gamma imaging or molecular breast imaging is technetium 99m (Tc 99m) sestamibi.

The 2013 Breast Imaging Reporting and Data System (BI-RADS) breast assessment and breast tissue categories are summarized in Table PG1.

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

Grading Schema	Category
Assessment categories	
	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

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

BI-RADS: Breast Imaging Reporting and Data System.
The most commonly used radiopharmaceuticals for sentinel lymph node detection using either lymphoscintigraphy or hand-held gamma detection include Tc 99m-labeled colloids (eg, sulfur colloid).

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Background/Overview

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 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 the TEC Special Report [2013]).

Scintimammography

Scintimammography is a diagnostic modality using radiopharmaceuticals to detect breast tumors. After intravenous injection of a radiopharmaceutical, the breast is evaluated using planar imaging. Scintimammography is performed with the patient lying prone, and the camera positioned laterally, which increases the distance between the breast and the camera. Special camera positioning to include the axilla may be included when the area of interest is an 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

BSGI and MBI were developed to address the poor resolution of conventional gamma cameras. 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 compress

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it lightly. The maximum distance between the detector and the breast is therefore from the surface to the midpoint of the breast. The radiotracer typically used is technetium 99m (Tc 99m) sestamibi, and MBI takes approximately 40 minutes.

Lymphoscintigraphy and Hand-Held Gamma Detection
Preoperative lymphoscintigraphy and/or intraoperative hand-held gamma detection of sentinel lymph nodes is a method of identifying sentinel lymph nodes for a biopsy after radiotracer injection. Surgical removal of one or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer. Several trials have compared outcomes following sentinel lymph node biopsy with axillary lymph node dissection for managing patients who have breast cancer. The National Surgical Adjuvant Breast and Bowel Project trial B-32 examined whether sentinel lymph node dissection 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. An additional three-year follow-up of morbidity after surgical node dissection revealed lower morbidity in the sentinel lymph node dissection group, including lower rates of arm swelling, numbness, tingling, and fewer early shoulder abduction deficits. A recent systematic review and meta-analysis by Ram et al (2014) reported no significant difference in overall survival (hazard ratio, 0.94; 95% confidence interval, 0.79 to1.19), no significant difference in disease-free survival (hazard ratio, 0.83; 95% confidence interval, 0.60 to 1.14), and similar rates of locoregional recurrence. 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 Tc 99m sestamibi. The product label states that Tc 99m sestamibi is "indicated for planar imaging as a second-line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass. Technetium Tc-99m sestamibi is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and it is not an alternative to biopsy."

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

Lymphoscintigraphy and/or Hand-Held Gamma Detection
The primary radiopharmaceuticals used for lymphoscintigraphy include Tc 99m pertechnetate-labeled colloids and Tc 99m tilmanocept (Lymphoseek). Whereas, Tc 99m sulfur colloid may frequently be 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 American College of Radiology, 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 the American College of Radiology, at these levels, BSGI is not indicated for breast cancer screening.

According to a study by Hruska and O'Connor (2015; who reported 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 to 300 MBq (6.5-8 mCi) of Tc 99m sestamibi that is made feasible with newer dual-head MBI systems, is 2.0 to 2.5 mSv. For comparison, the effective dose (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. The authors compared this dose with the estimated annual background radiation, which varies worldwide between 2.5 mSv and 10 mSv, and asserted that the effective dose from MBI "is considered safe for use in routine screening."

Hendrick (2010) calculated mean glandular doses and lifetime attributable risks of cancer due to film mammography, digital mammography, BSGI, and positron emission mammography (PEM). The author, a consultant to GE Healthcare and a member of the medical advisory boards of Koning (manufacturer of dedicated breast computed tomography) and Bracco (magnetic resonance contrast agents), used group risk estimates from the Biological Effects of Ionizing Radiation VII report to assess the risk of radiation-induced cancer and mortality from breast imaging studies. For a patient

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with average-sized breasts (compressed thickness during mammography of 5.3 cm per breast), estimated lifetime attributable risks of cancer at age 40 were:

- 5 per 100000 for digital mammography (breast cancer only),
- 7 per 100000 for screen-film mammography (breast cancer only),
- 55 to 82 per 100000 for BSGI (depending on the dose of Tc 99m sestamibi), and
- 75 for 100000 for PEM.

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

- 1.3 per 100000 for digital mammography (breast cancer only),
- 1.7 per 100000 for screen-film mammography (breast cancer only),
- 26 to 39 per 100000 for BSGI, and
- 31 for 100000 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 addressed in this review.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Several scintillation (gamma) cameras have been cleared for marketing by the FDA through the 510(k) process for "measuring and imaging the distribution of radionuclides in the human body by means of photon detection." Examples of gamma cameras used in BSGI are the Dilon 6800®‡ (Dilon Technologies) and single-head configurations of Discovery NM750b (GE Healthcare). Dual-head cameras used in MBI include LumaGEM™‡ (Gamma Medical) (FDA product code IYX) and Discovery NM750b (GE Healthcare).

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Tc-99m sestamibi (marketed by Draxis Specialty Pharmaceuticals, Cardinal Health 14, Mallinckrodt, and Pharmalucence) has been approved by the FDA with the following labeling: "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 2013, Tc 99m tilmanocept (Lymphoseek; Navidea Biopharmaceuticals) was approved by the FDA for use in breast cancer and melanoma as a radioactive diagnostic imaging agent to help localize lymph nodes.

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

In 2018, the 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.

Rationale/Source

Scintimammography, BSGI, and MBI use radiotracers with nuclear medicine imaging as a diagnostic tool for abnormalities of the breast. These tests are distinguished by the use of differing gamma camera technology, which may improve diagnostic performance for detecting small lesions. BSGI uses a 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 a biopsy after radiotracer injection. Surgical removal of one or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer.

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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. The relevant outcomes are overall survival (OS), 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. The relevant outcomes are OS, 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. The relevant outcomes are OS, 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

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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. The relevant outcomes are OS, 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. The relevant outcomes are OS, 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 three studies and a meta-analysis. The relevant outcomes are OS, disease-specific survival, test validity, and treatment-related morbidity. A meta-analysis and three 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.

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Supplemental Information

Practice Guidelines and Position Statements

Society of Nuclear Medicine
The Society of Nuclear Medicine (2010) released a procedure guideline on breast scintigraphy using breast-specific gamma cameras. The guideline was based on consensus, not on a systematic review of the literature or assessment of study quality, and most of it discusses 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
The American College of Obstetricians and Gynecologists (2017) updated its 2011 practice bulletin on breast cancer screening in average-risk women. There was no discussion or recommendation for scintimammography or any other gamma imaging techniques for routine screening.

American College of Radiology
Appropriateness Criteria from the American College of Radiology rated breast-specific gamma imaging a 1 or 2 (indicating "usually not appropriate" for breast cancer screening), in patients with high or intermediate breast cancer risk (last reviewed in 2016), palpable breast masses (last reviewed in 2017), and workup of breast pain (last reviewed in 2016). New guidelines on screening for breast cancer in above average-risk patients (last reviewed in 2017) do not mention breast-specific gamma imaging.

The American College of Radiology (2018) issued guidelines on the use of MBI for breast cancer screening. The guidelines state, “further advances in detector technology to allow lower dosing, more widespread penetration of MBI-guided biopsy capabilities, and additional large prospective trials (to include incidence screening results) will be needed before MBI can be embraced as a screening tool, even in women at elevated risk.”

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. The recommendations were based

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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.2.2019) 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. 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.1.2019) 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."

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

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Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review 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 2020
NCT02556684	A Prospective Study to Evaluate Dynamic Breast-Specific Gamma Imaging in Monitoring Tumor Responses in Patients With Locally Advanced Breast Cancer Undergoing Neoadjuvant Chemotherapy	200	Oct 2020
NCT02744053	Multimodality Breast Imaging for the Assessment of Tumor Response to Neoadjuvant Chemotherapy in Triple Negative Breast Cancer Patients	100	Nov 2021

NCT: national clinical trial.

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Policy History

Original Effective Date: 09/17/2014
Current Effective Date: 12/14/2020

09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. New policy.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. New policy statement added for gamma detection following radiopharmaceutical administration for localization of sentinel lymph nodes.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. No change to coverage.

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Scintimammography and Gamma Imaging of the Breast and Axilla

Policy # 00438
Original Effective Date: 09/17/2014
Current Effective Date: 12/14/2020

11/07/2019 Medical Policy Committee review
11/13/2019 Medical Policy Implementation Committee approval. No change to coverage.
11/05/2020 Medical Policy Committee review
11/11/2020 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 11/2021

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	78800, 78801, 78803

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HCPCS	S8080
ICD-10 Diagnosis	All related diagnoses

*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:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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