

Dopamine Transporter Single-Photon Emission Computed Tomography

Policy # 00496

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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.

Note: Deep Brain Stimulation is addressed separately in medical policy 00024.

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 dopamine transporter imaging with single-photon emission computed tomography to be **eligible for coverage**** when used for individuals with:

- Clinically uncertain Parkinson disease following evaluation by a neurologist or movement disorder specialist, i.e., unusual clinical features, incomplete or uncertain responsiveness to dopaminergic medication, or clinical diagnostic uncertainty; or
- Clinically uncertain dementia with Lewy bodies following evaluation by a specialist in dementia disorders, i.e., individuals with signs of dementia and suggestion of parkinsonism with motor abnormalities, or early hallucinations.

When 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 use of dopamine transporter imaging with single-photon emission computed tomography for all other indications not included above to be **investigational.***

Policy Guidelines

In July 2021, aducanumab (Aduhelm™; Biogen)‡ received U.S. Food and Drug Administration (FDA) accelerated approval and in July 2023, lecanemab-irmb (Leqembi®; Esai)‡ received FDA approval as amyloid beta-targeted antibodies for the treatment of mild cognitive impairment or mild

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dementia due to Alzheimer disease. A third anti-amyloid antibody product, donanemab-azbt, was approved by the FDA in July 2024. Aducanumab was subsequently discontinued by the manufacturer in 2024. The safety and efficacy of aducanumab, lecanemab, or donanemab in individuals with dementia with Lewy bodies has not been established as participants with any medical or neurological condition other than Alzheimer disease that might be a contributing cause to the subject's cognitive impairment were excluded from trials. The use of dopamine transporter imaging with single-photon emission computed tomography for the diagnosis, management, or surveillance of Alzheimer disease is considered out of scope for this policy.

Background/Overview

Parkinsonian Syndromes

Parkinsonian syndromes are a group of diseases that share similar cardinal signs, characterized by bradykinesia, rigidity, resting tremor, and gait disturbance. Parkinson disease (PD) is the most common cause of parkinsonism.

Despite the well-known symptoms of PD, diagnosis is challenging even for experienced clinicians, particularly in the early stages of the disease. In addition, other etiologies such as essential tremor, corticobasal degeneration, multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism, and drug-induced parkinsonism can lead to a similar set of symptoms. One recent approach to improve the accuracy of clinical diagnosis of PD and other parkinsonian syndromes is to evaluate the integrity of dopaminergic pathways in the brain using dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) imaging.

Dementia with Lewy Bodies

Dementia with Lewy bodies is a type of dementia characterized by parkinsonism, visual hallucinations, cognitive fluctuation, sleep disorders, and severe neuroleptic sensitivity. Dementia with Lewy bodies is the second most common form of degenerative dementia; Alzheimer disease, which can have similar symptoms at onset, is the most common.

Diagnosis can be challenging, particularly when patients have multiple comorbidities including cerebrovascular disease and/or Alzheimer disease. As with PD, dementia with Lewy bodies is characterized by the degeneration of nigrostriatal neurons; as such, DaT-SPECT is also proposed to differentiate dementia with Lewy bodies from Alzheimer disease.

Dopamine Transporter Imaging with Single-photon Emission Computed Tomography (DaT-SPECT)

DaT-SPECT is based on the selective affinity of dopamine transporter (DaT) ligands for dopamine-synthesizing neurons, which allows visualization of deficits in the nigrostriatal dopaminergic pathway.



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DaT ligands include iodine 123I-2β-carbomethoxy-3β-(4-iodophenyl) tropane (¹²³I-β-CIT), which is a cocaine analogue with an affinity for both dopamine and serotonin transporters. Intravenous ¹²³I-β-CIT requires a delay between injection and scan of about 24 hours. Iodine-123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (¹²³I-FP-CIT) is a fluoropropyl derivate of β-CIT that is selective for brain striatal DaT but can also bind to the serotonin transporter. Intravenous ¹²³I-FP-CIT can be injected 3 to 6 hours before the scan (DaTscan). Other SPECT ligands with affinity for dopamine transporter include technetium 99m (2β((N,Nϵ-bis(2-mercaptoethyl) ethylene diamino)methyl) and 3β-(4-chlorophenyl) tropane (^{99m}Tc-TRODAT-1).

Binding of ligands with an affinity for DaT ligands in the striatum is, in general, reduced in PD, genetic parkinsonism, dementia with Lewy bodies, corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy. In contrast, striatal DaT ligand binding is expected to be within the normal range of Alzheimer disease, essential tremor, dystonic tremor, orthostatic tremor, drug-induced parkinsonism, and psychogenic parkinsonism.

Visualization of striatal dopamine transporter binding, through DaT-SPECT, permits assessment of presynaptic dopaminergic deficit. It is proposed that an abnormal DaT-SPECT scan supports the diagnosis of PD, dementia with Lewy bodies, or other neurodegenerative parkinsonian syndromes, while a normal DaT-SPECT scan in a symptomatic patient supports the diagnosis of a disease not affecting the nigrostriatal dopaminergic pathway.

Analysis of DaT-SPECT images can be visual, semiquantitative, or quantitative. In patients with PD, physical symptoms start after 30% to 50% of dopaminergic neurons have degenerated. Symptomatic patients with PD would be thus expected to have sufficient abnormality on DaT-SPECT for visual analysis to be adequate for interpretation. A variety of methods are being tested to improve the validity and reliability of ratings, including commercially available software to define the region of interest for analysis and the development of an atlas for visual interpretation. Several research centers are developing quantitative and semiquantitative classification methods for the evaluation of DaT-SPECT images.

Anatomic variation in the brain, including vascular lesions, may interfere with the distribution of the iodine-123 tracer and could result in an abnormal scan. Dopamine agonists and levodopa may also affect DaT expression, which could influence the ability of DaT-SPECT to monitor the progression of disease unless these agents are discontinued prior to imaging. Patients with clinically diagnosed PD or dementia with Lewy bodies, who present with a normal DaT-SPECT scan, are referred to in the literature as having "scans without evidence of dopaminergic deficit." While many of these patients are ultimately diagnosed with non-PD syndromes, a portion of patients with normal DaT-SPECT imaging are confirmed to have PD or dementia with Lewy bodies by the reference standard. In studies where clinical diagnosis is used as an endpoint, scans without evidence of dopaminergic deficit are present in 3% to 20% of PD patients. In a study of patients clinically diagnosed with



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dementia with Lewy bodies, van der Zande et al (2016) found that 10% of these patients had normal scans. Further research may shed light on these cases.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 2011, DaTscanTM‡ (GE Healthcare) was approved by the U.S. Food Drug Administration (FDA) through a new drug application and is "indicated for striatal dopamine transporter visualization using single-photon emission computed tomography brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes. In these patients, DaTscan may be used to help differentiate ET [essential tremor] from tremor due to parkinsonian syndromes (idiopathic Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations." In 2022, DaTscan was approved for use in patients with suspected dementia with Lewy bodies.

In July 2021, aducanumab (AduhelmTM; Biogen)‡, an amyloid beta-targeted antibody, was approved for the treatment of mild cognitive impairment or mild dementia due to Alzheimer disease. In July 2023, lecanemab-irmb (Leqembi[®]; Esai)‡ received FDA approval as amyloid beta-targeted antibodies for the treatment of mild cognitive impairment or mild dementia due to Alzheimer disease. A third anti-amyloid antibody product, donanemab-azbt, was approved by the FDA in July 2024. Aducanumab was subsequently discontinued by the manufacturer in 2024. The safety and efficacy of aducanumab, lecanemab, or donanemab in patients with dementia with Lewy bodies has not been established as patients with any medical or neurological condition other than Alzheimer disease that might be a contributing cause to the subject's cognitive impairment were excluded from trials. The use of DaT-SPECT for the diagnosis, management, or surveillance of Alzheimer disease is considered out of scope for this policy.

FDA product code: KPS.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), using radiopharmaceutical ioflupane injection, is a neuroimaging modality being evaluated to improve the differential diagnosis of parkinsonian syndromes from nonparkinsonian tremor, as well as dementia with Lewy bodies from Alzheimer disease.



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Summary of Evidence

For individuals who have clinically uncertain Parkinson disease (PD) who receive dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), the published evidence includes randomized controlled trials (RCTs), cohort studies, and case series. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. In populations with clinically apparent PD, studies of diagnostic accuracy have reported high sensitivity and specificity for PD. Studies of clinical validity in the target population of clinically uncertain PD are limited by gaps in study design, conduct, and relevance. Evidence on clinical utility in the target population includes an RCT showing no significant difference in outcomes over time between patients who received a DaT-SPECT scan and those who did not. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have clinically uncertain dementia with Lewy bodies who receive DaT-SPECT, the published evidence includes RCTs, cohort studies, and case series. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. No studies with the optimal reference standard to assess clinical validity have been performed in the target population of clinically uncertain dementia with Lewy bodies. No studies have directly evaluated the effect of DaT-SPECT on health outcomes in the target population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

2018 Input

Clinical input was sought to help determine whether the use of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) in individuals with clinically uncertain Parkinson disease (PD) or clinically uncertain dementia with Lewy bodies would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses identified through specialty societies.

In individuals who have clinically uncertain PD who receive DaT-SPECT, clinical input supports that DaT-SPECT is clinically useful when a negative result on DaT-SPECT is used to inform treatment decisions by reducing or avoiding unnecessary dopaminergic therapy. Clinical input highlights that the published randomized controlled trial also reported changes in management following DaT-SPECT imaging that may translate to improvements in health outcomes over time, and the 1 year study follow-up may be too short to demonstrate significant improvement in quality of life in a slowly progressive disease such as PD. Clinical input further supports that DaT-SPECT offers clinically valid diagnostic information about the presence or absence of functional loss in the



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dopamine system (ie, nigrostriatal degeneration) and is clinically useful for clinically uncertain Parkinsonian syndrome when a negative result on DaT-SPECT is used to inform treatment decisions by reducing or avoiding unnecessary dopaminergic therapy.

In individuals who have clinically uncertain dementia with Lewy bodies who receive DaT-SPECT, clinical input supports that DaT-SPECT is clinically useful when a positive result on DaT-SPECT is used to inform treatment decisions by avoiding potentially harmful use of neuroleptics which may be used in dementia patients. Clinical input noted that DaT-SPECT offers clinically valid diagnostic information about the presence or absence of functional loss in the dopamine system (ie, nigrostriatal degeneration) and is clinically useful for clinically uncertain dementia with Lewy bodies using a chain of evidence where a positive result on DaT-SPECT is used to inform treatment decisions by avoiding potentially harmful use of neuroleptics typically used in dementia patients.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology

In 2019, the American College of Radiology updated the appropriateness criteria for movement disorders and neurodegenerative diseases. The College categorized Ioflupane SPECT/computed tomography (CT) as 'may be appropriate' for initial imaging of Parkinsonian syndrome. A strength of evidence rating was not given for this statement.

The American College of Radiology (2019) updated the appropriateness criteria for dementia. The College categorized Ioflupane SPECT or SPECT/CT brain as 'may be appropriate' for initial imaging for suspected dementia with Lewy bodies. A strength of evidence rating was not given for this statement.

Dementia of Lewy Bodies Consortium

In 2017, the Dementia of Lewy Bodies Consortium published clinical guidelines on diagnosis and management based on American expert opinion. The guidelines stated that reduced DaT uptake in basal ganglia demonstrated by SPECT is an indicative biomarker. As such, dementia with abnormal DaT-SPECT imaging would be classified as possible dementia with Lewy bodies. The presence of another core clinical feature (fluctuating cognition, recurrent visual hallucinations, rapid-eye-movement sleep disorder, parkinsonism motor abnormalities) in addition to dementia and abnormal DaT-SPECT imaging would allow classification as probable dementia with Lewy bodies. It was noted that patients with autopsy-confirmed dementia with Lewy bodies may have normal DaT-SPECT imaging.



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Movement Disorders Society

In 2015, the Movement Disorders Society (MDS) published diagnostic criteria for PD intended for use in clinical research but also commonly used to guide clinical diagnosis. The MDS considers the clinical expert opinion to be the criterion standard to diagnose PD and that diagnoses are usually made clinically without ancillary diagnostic testing. Methods that may become available as knowledge advances are diagnostic biochemical markers, anatomic neuroimaging, and methods to detect alpha-synuclein deposition. Normal functional neuroimaging of the presynaptic dopaminergic system, if performed, is listed as an absolute exclusion criterion for PD. MDS noted that, although dopaminergic neuroimaging can help to distinguish parkinsonism from PD mimics like essential tremor, "it does not qualify as a criterion for the differentiation of PD from other parkinsonian conditions like atypical parkinsonian syndromes." Normal functional neuroimaging of the presynaptic dopaminergic system is also listed as criteria for exclusion from diagnosis of PD in patients with early/de novo PD.

In 2023, the MDS published a statement on the biological definition, staging and classification of PD. The document mentions dopamine imaging but states that its use is not widespread enough to be included in a staging or classification schema.

National Institute for Health and Care Excellence

In 2006, the NICE published guidance on the diagnosis and management of PD, which was updated in 2017. The 2006 guidance stated that iodine 123 N-(3-fluoropropyl)-2 β -carbomethoxy-3 β -(4-iodophenyl) nortropane (¹²³I-FP-CIT) SPECT should be considered for people with tremor where essential tremor cannot be clinically differentiated from parkinsonism (based on studies with a level of evidence 1a or 1b); this recommendation is continued in 2017 guidance. Also unchanged was the recommendation that ¹²³I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation (based on the level of evidence IV, expert opinion).

The NICE updated its 2016 guidance on dementia in 2018. It recommended that ¹²³I-FP-CIT SPECT be used to help establish the diagnosis in those with suspected DLB [dementia with Lewy bodies] if the diagnosis is uncertain.

Society of Nuclear Medicine and Molecular Imaging et al

In 2020, the Society of Nuclear Medicine and Imaging and the European Association of Nuclear Medicine published a joint practice guideline and procedure standard for dopaminergic imaging in Parkinsonian syndromes. The guideline indicated presynaptic dopaminergic imaging for "detecting loss of nigrostriatal dopaminergic neuron terminals of patients with parkinsonian syndromes, especially:

- To support the differential diagnosis between essential tremor and neurodegenerative parkinsonian syndromes. Note that presynaptic dopaminergic imaging is unable to distinguish IPD [idiopathic Parkinson disease] and DLB from PSP [progressive



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supranuclear palsy], CBD [corticobasal degeneration], or putaminal variant of MSA [multiple system atrophy];

- To help distinguish between dementia with Lewy bodies and other dementias (in particular, Alzheimer's disease, AD);
- To support the differential diagnosis between parkinsonism due to presynaptic degenerative dopamine deficiency and other forms of parkinsonism, e.g., between IPD and drug-induced, psychogenic, or vascular parkinsonism;
- To detect early presynaptic parkinsonian syndromes."

In 2011, the Society of Nuclear Medicine, now called the Society of Nuclear Medicine and Molecular Imaging, provided practice guidelines for DaT-SPECT. The guidelines stated that the main indication for DaT-SPECT is striatal DaT visualization in the evaluation of adults with suspected parkinsonian syndromes to help differentiate essential tremor from tremor due to presynaptic parkinsonian syndromes (PD, multisystem atrophy, progressive supranuclear palsy). Other indications are the early diagnosis of presynaptic parkinsonian syndromes, differentiation of presynaptic parkinsonian syndromes from parkinsonism without a presynaptic dopaminergic loss (eg, drug-induced parkinsonism, psychogenic parkinsonism), and differentiation of dementia with Lewy bodies from AD. The guidance stated that visual interpretation of the scan is usually sufficient for clinical evaluation, where the striatal shape, extent, symmetry, and intensity differentiate normal from abnormal. For semiquantitative analysis, each site should establish its own reference range by scanning a population of healthy controls or by calibrating its procedure with another center that has a reference database.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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
<i>Ongoing</i>			



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NCT01453127	DaTSCAN Imaging in Aging and Neurodegenerative Disease	500	Dec 2025
NCT02305147	Cohort Study to Identify Predictor Factors of Onset and Progression of Parkinson's Disease (ICEBERG)	360	Nov 2024
<i>Unpublished</i>			
NCT04193527 ^a	A Multicentre, Phase 3, Clinical Study to Compare the Striatal Uptake of a Dopamine Transporter Radioligand, DaTSCAN TM Ioflupane (123I) Injection, After Intravenous Administration to Chinese Patients With a Diagnosis of Parkinson's Disease, Multiple System Atrophy, Progressive Supranuclear Palsy, or Essential Tremor and to Healthy Controls	172	Dec 2021

NCT: national clinical trial.

^aDenotes industry sponsored or co-sponsored trial

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Policy # 00496

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| 04/07/2016 | Medical Policy Committee review |
| 04/20/2016 | Medical Policy Implementation Committee approval. New policy. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 04/06/2017 | Medical Policy Committee review |
| 04/19/2017 | Medical Policy Implementation Committee approval. No change to coverage. |
| 04/05/2018 | Medical Policy Committee review |
| 04/18/2018 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/10/2019 | Medical Policy Committee review |
| 01/23/2019 | Medical Policy Implementation Committee approval. Policy statement changed to eligible for coverage for clinically uncertain Parkinson disease and clinically uncertain dementia with Lewy bodies. |
| 01/03/2020 | Medical Policy Committee review |
| 01/08/2020 | Medical Policy Implementation Committee approval. No change to coverage. |
| 02/04/2021 | Medical Policy Committee review |
| 02/10/2021 | Medical Policy Implementation Committee approval. No change to coverage. Criteria specialist clarified. |
| 02/03/2022 | Medical Policy Committee review |
| 02/09/2022 | Medical Policy Implementation Committee approval. No change to coverage. |
| 02/02/2023 | Medical Policy Committee review |
| 02/08/2023 | Medical Policy Implementation Committee approval. No change to coverage. |
| 02/01/2024 | Medical Policy Committee review |
| 02/14/2024 | Medical Policy Implementation Committee approval. No change to coverage. Title changed from Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography to Dopamine Transporter Single-Photon Emission Computed Tomography. |
| 02/06/2025 | Medical Policy Committee review |
| 02/12/2025 | Medical Policy Implementation Committee approval. No change to coverage |
- Next Scheduled Review Date: 02/2026



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Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	78803
HCPCS	A9584
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



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diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with 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.

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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

