BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Dopamine Transporter Imaging with Single Photon Emission Computed Tomography (DAT-SPECT)

Policy #: 504
Latest Review Date: November 2023
Category: Radiology

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after October 9, 2020:

Blue Advantage will treat **dopamine transporter imaging with single photon emission computed tomography (DaT-SPECT)** as a **covered benefit** when used for individuals with:

- clinically uncertain Parkinson disease (PD); **OR**
- clinically uncertain dementia with Lewy bodies

Blue Advantage will treat the use of **dopamine transporter imaging with single-photon emission computed tomography** as a **non-covered benefit** and as **investigational** for all other indications not included above.

Note: In July 2021, aducanumab (Aduhelm™; Biogen), received FDA accelerated approval and in July, 2023, lecanemab-irmb- (Leqembi; Esai) received FDA approval as amyloid beta-targeted antibodies was approved for the treatment of mild cognitive impairment or mild dementia due to Alzheimer disease. The safety and efficacy of aducanumab or lecanemab 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.

Effective for dates of service prior to October 9, 2020:

Blue Advantage will treat **dopamine transporter imaging with single photon emission computed tomography (DaT-SPECT)** as a **noncovered benefit** and as **investigational** for **all indications**, including but not limited to:

- aiding in the diagnosis of patients with clinically uncertain parkinsonian syndromes; **OR**
- distinguishing between parkinsonian syndromes and essential tremor; OR
- distinguishing between dementia with Lewy bodies and Alzheimer disease; OR
- monitoring of disease progression

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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

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 early stages of the disease. In addition, other etiologies such as essential tremor, corticobasal degeneration, multisystem atrophy, progressive supranuclear palsy, vascular parkinsonism, and drug-induced parkinsonism can lead to a similar set of symptoms.

One recent approach to improve the accuracry of clinical diagnosis of PD and other parkinsonian syndromes is to evaluate the integrity of dopaminergic pathways in the brain using DaT-SPECT imaging.

Dementia with Lewy Bodies

Dementia with Lewy Bodies (DLB) is a type of dementia characterized by Parkinsonism, visual hallucinations, cognitive fluctuation, sleep disorders, and severe neuroleptic sensitivity. DLB 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, DLB is characterized by the degeneration of nigrostriatal neurons; as such, DaT-SPECT is also proposed to differentiate DLB from Alzheimer disease.

Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography (DaT-SPECT)

Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) is based on the selective affinity of dopamine transporter ligands for dopamine synthesizing neurons, which allows visualization of deficits in the nigrostriatal dopaminergic pathway.

Dopamine transporter ligands include iodine 123 2β-carbomethoxy-3β-(4-iodophenyl) tropane (123 I-β-CIT), which is a cocaine analogue with affinity for both dopamine transporter 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 dopamine transporter, but can also bind to the serotonin transporter. Intravenous 123I-FP-CIT can be injected three to six hours before the scan (DaTscan). Other ligands with affinity for dopamine

transporter include technetium 99m (2β ((N, N`-bis (2-mercaptoethyl) ethylene diamino) methyl) and 3β-(4-chlorophenyl) tropane (99mTc-TRODAT-1).

Binding of ligands with an affinity for DaT ligands in the striatum is, in general, reduced in PD, genetic parkinsonism, DLB, 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, DLB, 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 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 impede the distribution of the iodine123 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 DLB, 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 DLB by the reference standard. In studies where clinical diagnosis is used as an end point, scans without evidence of dopaminergic deficit are present in 3% to 20% of PD patients. In a study of patients clinically diagnosed with DLB, van der Zande et al (2016) found that 10% of these patients had normal scans. Further research may shed light on these cases.

KEY POINTS:

The most recent literature review was updated through August 28, 2023.

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

studies. 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 technologyresults in an improvement in the net health outcomes.

For individuals who have clinically uncertain dementia with Lewy bodies who receive DaT-SPECT, the published evidence includes RCTs, cohort studies, and case series studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. No such 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 outcomes.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
2018 Input
Clinical input was sought to help determine whether the use of DaT-SPECT in individuals with clinically uncertain Parkinson disease 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 one specialty society-level response and two 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 RCT also reported changes in management following DaT-SPECT imaging that may translate to improvements in health outcomes over time, and the one-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 dopamine system (ie, nigrostriatal degeneration) and is clinically useful for clinically uncertain Parkinson 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

American Academy of Neurology

The practice parameters from the American Academy of Neurology (2006; reaffirmed 2013; retired 2018) stated that β-CIT (2β-carbomethoxy-3β-(4-iodophenyl) tropane) and IBZM (iodobenzamide) SPECT are possibly useful in distinguishing PD from essential tremor (5 class III studies).41, There was insufficient evidence to determine whether these modalities are useful in distinguishing PD from other forms of Parkinsonism.

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/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.44, 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.

Movement Disorder Society

The Movement Disorder Society's (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 need for ancillary diagnostic testing. Methods that may become available as knowledge advances are diagnostic biochemical markers, anatomic neuroimaging, and methods to detect alpha-synuclein deposition. 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."

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence published guidance on the diagnosis and management of PD in 2006, which was updated in 2017. The 2006 guidance stated that 123I-FP-CIT SPECT should be considered for people with tremor where essential tremor cannot be clinically differentiated from parkinsonism (based on studies with level of evidence 1a or 1b); this guidance is continued in 2017 recommendations. In addition, the 2006 guidance stated that 123I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation (based on level of evidence IV, expert opinion).

The Institute updated its 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 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. Preventative Service Task Force Recommendations
Not applicable

KEY WORDS:
DaTscan, DAT-SPECT, 123I-Ioflupane, Iodine I-123 ioflupane diagnostic study, dopamine transporter SPECT using 123I-Ioflupane, FP-CIT SPECT, [123I]-FP-CIT SPECT imaging

APPROVED BY GOVERNING BODIES:
In 2011, DaTscan™ (GE Healthcare, Chicago, IL) was approved by the U.S. Food Drug Administration 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 July 2021, aducanumab (Aduhelm™; Biogen), an amyloid beta-targeted antibody, was approved for the treatment of mild cognitive impairment or mild dementia due to Alzheimer disease. The safety and efficacy of aducanumab 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

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT Codes:

78803	Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); tomographic (SPECT)

HCPCS Codes:

A9584	Iodine I-123 ioflupane, diagnostic, per study dose, up to 5 millicuries

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POLICY HISTORY:

Adopted for Blue Advantage, August 2012
Available for comment September 18 through October 31, 2012
Medical Policy Group, July 2013
Medical Policy Group, July 2014
Medical Policy Group, November 2015
Medical Policy Group, September 2016
Medical Policy Group, November 2017
Medical Policy Group, December 2018
Medical Policy Group, October 2019
Medical Policy Group, December 2019: Annual Coding Update
Medical Policy Group, October 2020
Medical Policy Group, November 2020
Medical Policy Group, October 2021
Medical Policy Group, October 2022
Medical Policy Group, November 2023

common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.