Introduction

DAT-SPECT imaging is proposed as a way to look at certain brain functions. In this technique, a chemical containing a tiny amount of radioactivity is injected into a vein. Nerve cells (neurons) in the brain that are associated with dopamine take up this radioactivity. A special camera then captures images of the dopamine neurons. It’s known that there is a substantial decrease in the dopamine-producing neurons in Parkinson disease. DAT-SPECT may be medically necessary when a healthcare provider is clinically uncertain of a diagnosis of Parkinson syndrome or dementia with Lewy bodies. DAT-SPECT has also been studied for other conditions, such as essential tremor or Alzheimer disease. DAT-SPECT is considered investigational (unproven) in many situations. This policy describes when DAT-SPECT may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

Imaging | Medical Necessity
---|---
Dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) | Dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) may be considered medically necessary when used for individuals with:
- Clinically uncertain Parkinson disease
- Clinically uncertain dementia with Lewy bodies

Use of dopamine-transporter imaging with single-photon emission computed tomography is considered investigational for all other indications not included above.

Documentation Requirements
The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:
- Office visit notes that contain the relevant history and physical supporting:
  - Clinically uncertain Parkinson disease
  - Clinically uncertain dementia with Lewy bodies

Coding

<table>
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<td><strong>CPT</strong></td>
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<td>78607</td>
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<tr>
<td><strong>HCPCS</strong></td>
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<td>A9584</td>
<td>Iodine I-123 ioflupane, diagnostic, per study dose, up to 5 millicuries</td>
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Definition of Terms

Dopamine: An organic chemical that acts as a neurotransmitter in the brain and is involved with body movement. Destruction of dopamine neurons produces the symptoms of Parkinson's disease.

Parkinsonian syndromes (PS): A group of diseases that share similar fundamental symptoms of slow movement (bradykinesia), rigidity, tremor at rest, and trouble walking.

Evidence Review

Description

Dopamine transporter imaging with single-photon emission computed tomography (DAT-SPECT) using radiopharmaceutical ioflupane (I\textsuperscript{123}) injection is a neuro-imaging modality being evaluated to improve the differential diagnosis of parkinsonian syndromes from nonparkinsonian tremor, as well as dementia with Lewy bodies from Alzheimer disease.

Background

Parkinson Disease

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.

Diagnosis

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, multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism, and drug-induced parkinsonism can lead to a similar set of symptoms.

While the criterion standard is postmortem histopathology, clinical diagnosis may be used as an interim reference standard. The accuracy of the diagnosis is influenced by the duration of the symptoms and the clinician’s experience.¹ Even in specialized movement disorders centers, up to 25% of patients may be misclassified, and some patients (eg, those with essential tremor who have been diagnosed with PD) may be erroneously treated.² Such misclassifications have led to the call for additional diagnostic tests and biomarkers to improve the accuracy of clinical diagnosis of PD and other parkinsonian syndromes. One recent approach 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 (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**

Diagnosis can be challenging, particularly when patients have multiple comorbidities including cerebrovascular disease and/or Alzheimer disease.³ 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. Misdiagnosis of DLB is concerning, because some have noted a severe sensitivity (potentially life-threatening) to neuroleptics in patients with DLB. However, newer agents are usually well-tolerated, and patients with DLB may also respond to the cholinesterase inhibitors that are more commonly used to treat Alzheimer disease.

**DaT-SPECT**

DaT-SPECT is based on the selective affinity of DaT ligands for dopamine synthesizing neurons, which allows visualization of deficits in the nigrostriatal dopaminergic pathway.
DaT ligands include iodine 123 2β-carbomethoxy-3β-(4-iodophenyl) tropane (123I-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 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,N'-bis (2-mercaptoethyl) ethylene diamino)methyl) and 3β-(4-chlorophenyl) tropane (99mTc-TRODAT-1). Binding of ligands with 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 in 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 syndrome, 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 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 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.\textsuperscript{13} In a study of patients clinically diagnosed with DLB, van der Zande et al (2016) found that 10% of these patients had normal scans.\textsuperscript{14} Further research may shed light on these cases.

**Summary of Evidence**

The following conclusions are based on a view of the evidence, including, but not limited to, published evidence and clinical expert opinion, via BCBSA’s Clinical Input Process.

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

For individuals who have clinically uncertain dementia with Lewy bodies who receive DaT-SPECT, the published evidence includes randomized control trials, cohort studies, and case series studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. No such studies have been performed in the target population of clinically uncertain dementia with Lewy Bodies. No studies have directly evaluated the effect of DaT-SPECT imaging on health outcomes in the target population. Evidence reported through clinical input augments the published evidence by supporting 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 DLB 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

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

Table 1. Summary of Key Trials

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<th>Trial Name</th>
<th>Planned Enrollment</th>
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<td>Dec 2018</td>
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<td>NCT01141023</td>
<td>The Parkinson’s Progression Markers Initiative (PPMI)</td>
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NCT: national clinical trial.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various academic medical centers and specialty medical societies may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the academic medical centers or specialty medical societies, unless otherwise noted.

2018 Input

In response to requests, clinical input on use of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) for diagnosing clinically uncertain Parkinson disease and clinically uncertain dementia with Lewy bodies was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses.
identified through specialty societies including physicians with academic medical center affiliations, while this policy was under review in 2018.

Based on the evidence and independent clinical input, the clinical input supports that the following indications provide a clinically meaningful improvement in the net health outcome and are consistent with generally accepted medical practice:

- Use of DaT-SPECT for individuals with clinically uncertain Parkinson disease; or
- Use of DaT-SPECT for individuals with clinically uncertain dementia with Lewy bodies.

**2015 Input**

In response to requests, input was received from 1 physician specialty society and 3 academic medical centers (4 reviewers) while this policy was under review in 2015. Input on whether DaT-SPECT is considered to be medically necessary in the assessment of clinically uncertain parkinsonian syndromes or to differentiate between clinically uncertain parkinsonian syndromes and essential tremor was mixed. Most respondents did not consider DaT-SPECT to be medically necessary to differentiate between DLB and Alzheimer’s disease.

**2012 Input**

In response to requests, input was received from 3 physician specialty societies and 3 academic medical centers (6 reviewers) while this policy was under review in 2012. Input regarding the medical necessity of DaT-SPECT was mixed.

**Practice Guidelines and Position Statements**

**American College of Radiology**

The American College of Radiology (2015) published appropriateness criteria for dementia and movement disorders. The College stated that the diagnosis of idiopathic Parkinson disease (PD) is usually based on patient history and physical examination alone and that, when clinical signs and symptoms and response to medication are typical of PD, neuroimaging is not required. In patients with unusual clinical features, incomplete or uncertain medication responsiveness, or clinical diagnostic uncertainty, imaging to exclude alternative pathologies
may be indicated. The College has also stated that positron emission tomography and single-photon emission computed tomography (SPECT) tracer studies exploring the presynaptic nigrostriatal terminal function and the postsynaptic dopamine receptors have been unable to reliably classify the various parkinsonian syndromes; further, positron emission tomography and SPECT may not even be able to reliably measure disease progression. Use of dopamine transporter (DaT) imaging with SPECT was rated 5 (may be appropriate) to evaluate suspected dementia with Lewy bodies (DLB) and rated 3 (usually not appropriate) to evaluate PD with either typical or atypical clinical features.

**American Academy of Neurology**

The 2006 practice parameters (reaffirmed in 2013) from the American Academy of Neurology state that β-CIT and IBZM (iodobenzamide) SPECT are possibly useful in distinguishing PD from essential tremor (5 class III studies). There was insufficient evidence to determine whether these modalities are useful in distinguishing PD from other forms of parkinsonism.

**Society of Nuclear Medicine and Molecular Imaging**

The Society of Nuclear Medicine, now called the Society of Nuclear Medicine and Molecular Imaging (2011), 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, multiple-system 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 DLB from Alzheimer disease. 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.
**Movement Disorders Society**

The Movement Disorders Society’s (MDS) 2015 diagnostic criteria for PD are intended for use in clinical research but may be used to guide clinical diagnosis. MDS considers 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, anatomical neuroimaging, and methods to detect alpha-synuclein deposition. Normal functional neuroimaging of the presynaptic dopaminergic system, if performed, is listed as an absolute exclusion criteria 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.

**National Institute for Health and Clinical Evidence**

The National Institute for Health and Clinical Evidence (2006) published guidance on the diagnosis and management of PD, which was updated in 2017. The 2006 guidance stated that iodine 123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(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 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 level of evidence IV, expert opinion).

The Institute 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 if the diagnosis is uncertain.

**Dementia of Lewy Bodies Consortium**

The Dementia of Lewy Bodies Consortium (2017) 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 DLB. 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 DLB. It was noted that patients with autopsy-confirmed DLB may have normal DaT-SPECT imaging.

**Medicare National Coverage**

There is no national coverage determination.

**Regulatory Status**

In 2011, DaTscan™ (GE Healthcare) 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.”

FDA product code: KPS.

**References**


### History

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<th>Comments</th>
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<td>09/27/13</td>
<td>Policy updated with literature review through May 28, 2013; references 19 and 23 added; policy statement unchanged.</td>
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<td>09/23/14</td>
<td>Annual Review. Policy updated with literature review through June 6, 2014; reference 6 added; policy statement unchanged.</td>
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<td>01/01/19</td>
<td>Annual Review, approved December 13, 2018. Policy updated with literature review through August 2018. Policy updated with clinical input and change to policy statements to medically necessary for clinically uncertain Parkinson disease and clinically uncertain dementia with Lewy bodies; reference 39 added; references 26 and 43 updated.</td>
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Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
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