MEDICAL POLICY – 6.01.54

Dopamine Transporter Imaging with Single-Photon Emission Computed Tomography

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 is being studied to see whether it can be used to diagnose Parkinson or other conditions that cause tremors, like essential tremor. This technique is considered investigational (unproven). More studies are needed to find out whether this technique can be reliably used to distinguish between or diagnose certain conditions.

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.
### Imaging

**Dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT)**

**Investigational**

Dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) is investigational for all indications, including but not limited to:

- Aiding in the diagnosis of patients with clinically uncertain parkinsonian syndromes
- Distinguishing between parkinsonian syndromes and essential tremor
- Distinguishing between dementia with Lewy bodies and Alzheimer disease
- Monitoring of disease progression

### Coding

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<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.

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**Evidence Review**

**Description**

Dopamine transporter imaging with single-photon emission computed tomography (DAT-SPECT) using radiopharmaceutical ioflupane \( ^{123} \text{I} \) 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 (DLB) from Alzheimer disease (AD).

**Background**

*Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography*

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 2\( \beta \)-carbomethoxy-3\( \beta \)-(4-iodophenyl) tropane \( ^{123} \text{I-} \beta \)-CIT), which is a cocaine analogue with affinity for both dopamine transporter and serotonin transporters. Intravenous \( ^{123} \text{I-} \beta \)-CIT requires a delay between injection and scan of about 24 hours. Iodine 123 N-(3-fluoropropyl)-2\( \beta \)-carbomethoxy-3\( \beta \)-(4-iodophenyl)nortropane \( ^{123} \text{I-FP-CIT} \) is a fluoropropyl derivate of \( \beta \)-CIT that is selective for brain striatal dopamine transporter, but can also bind to the serotonin transporter. Intravenous \( ^{123} \text{I-FP-CIT} \) can be
injected 3 to 6 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 affinity and specificity for dopamine transporter ligands in the striatum is, in general, reduced in Parkinson disease (PD), genetic parkinsonism, dementia with Lewy bodies (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, psychogenic parkinsonism, and vascular 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. There are, however, a significant percentage of patients with clinically diagnosed PD who do not show reduced DAT-SPECT binding. Scans without evidence of dopaminergic deficit are referred to as SWEDD. Additional research may shed light on these cases.

Analysis of DAT-SPECT images can be visual, semiquantitative, or quantitative. Because patients typically do not become symptomatic before a substantial number of striatal synapses have degenerated, visual interpretation of the scan is thought to be sufficient for clinical evaluation. 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.

**Diagnosis of Parkinson Disease**

Parkinsonian syndromes (PS) 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 (ET), corticobasal degeneration, multisystem 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. Accuracy of the diagnosis is influenced by the duration of the
symptoms, in addition to the clinician's experience. 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. 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 DAT-SPECT imaging.

**Diagnosis of Dementia with Lewy Bodies (DLB)**

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. 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.

**Summary of Evidence**

For individuals who have clinically uncertain Parkinson disease (PD) who received dopamine transporter single-photon emission computed tomography (DAT-SPECT), the evidence includes randomized controlled trials, cohort studies, and case series studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. Studies of technical validity have shown good interobserver reliability in interpreting images. 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 have reported moderate sensitivity and high specificity. These findings are dependent on a reference standard (clinical diagnosis over time), and it is unknown whether DAT-SPECT would show greater sensitivity when assessed by the criterion standard (histopathologic diagnosis). 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have clinically uncertain dementia with Lewy bodies (DLB) who receive DAT-SPECT, the evidence includes randomized control trials, cohort studies, and case series studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. Relative to the criterion end point of histopathology, DAT-SPECT has lower sensitivity and higher specificity than expert clinical diagnosis in patients with likely dementia with Lewy bodies. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

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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<td>The Parkinson's Progression Markers Initiative (PPMI)</td>
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<td>NCT01453127</td>
<td>DaTSCAN Imaging in Aging and Neurodegenerative Disease</td>
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<td>NCT01767818</td>
<td>Longitudinal, Single-center Prospective Study to Assess</td>
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<td></td>
<td>Progression of Clinical Features and Biologic Markers of Parkinson's Disease Subjects of Varying Levels of Disease Severity</td>
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NCT: national clinical trial.
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

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

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 (ACR) has published appropriateness criteria for dementia and movement disorders, last reviewed in 2015. ACR has 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. ACR has also stated that positron emission tomography (PET) and SPECT tracer studies exploring the presynaptic nigrostriatal terminal function and the
postsynaptic dopamine receptors have been unable to reliably classify the various parkinsonian syndromes and may not reliably measure disease progression. Use of DAT-SPECT was rated 5 (may be appropriate) to evaluate suspected 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 July 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 if 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, provided practice guidelines for DAT imaging with SPECT in 2011. The guidelines stated that the main indication for DAT-SPECT is striatal DAT visualization in the evaluation of adult patients with suspected PS to help differentiate ET from tremor due to presynaptic PS (PD, multiple-system atrophy, progressive supranuclear palsy). Other indications are the early diagnosis of presynaptic PS, differentiation of presynaptic PS from parkinsonism without presynaptic dopaminergic loss (eg, drug-induced parkinsonism, psychogenic parkinsonism), and differentiation of DLB from AD. The guidance states 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) diagnostic criteria for PD from 2015 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 the need for ancillary diagnostic testing. Methods that may become available as knowledge advances are diagnostic biochemical markers, anatomical neuroimaging, and methods to detect alpha-synuclein deposition. MDS noted that, although dopaminergic
neuroimaging can help to distinguish parkinsonism from PD mimics like ET, “it does not qualify as a criterion for the differentiation of PD from other parkinsonian conditions like atypical parkinsonian syndromes.”

**European Federation of Neurological Societies and Movement Disorder Society**

The European Federation of Neurological Societies and Movement Disorder Society published joint recommendations for the diagnosis of PD in 2013. They provided a level A recommendation for the use of DAT-SPECT in the differential diagnosis between degenerative parkinsonism and ET. The guidelines specify that DAT-SPECT is indicated in the presence of significant diagnostic uncertainty and particularly in patients presenting atypical tremor manifestations.

**European Association of Nuclear Medicine**

The European Association of Nuclear Medicine updated its guidelines on procedures for DAT-SPECT in 2010, based on expert opinion in European countries. The guidelines stated that iodine 123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (123I-FP-CIT) imaging is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain parkinsonian syndrome and for the differentiation of DLB from other dementias. Other indications were the early diagnosis of neurodegenerative parkinsonism, assessment of disease severity, and differentiation of presynaptic parkinsonism from other forms of parkinsonism (eg, neuroleptic-induced parkinsonism). The guidelines stated that, in addition to visual interpretation, semiquantitative analysis is recommended to objectively assess striatal DaT binding. Issues requiring further clarification include the assessment of disease progression and effects of treatments and methods for operator-independent definition of region of interest.

**National Institute for Health and Clinical Evidence**

The National Institute for Health and Clinical Evidence (NICE) 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 ET 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 $^{123}$I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation (based on level of evidence IV, expert opinion); this too was unchanged in the 2017 update. The next expected update is April 2018. NICE updated its clinical guidelines on dementia in May 2016. It recommended that $^{123}$I-FP-CIT SPECT be used to help establish the diagnosis in those with suspected DLB if the diagnosis is in doubt.

**Dementia of Lewy Bodies Consortium**

The Dementia of Lewy Bodies Consortium published clinical guidelines on diagnosis and management in 2017, based on American expert opinion. The guidelines stated that reduced dopamine transporter 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. Presence of an additional core clinical feature (fluctuating cognition, recurrent visual hallucinations, REM 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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Status**

In 2011, DaTscan™ (GE Healthcare, Chicago, IL) 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 (SPECT) brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.”

FDA product code: KPS.


32. Tolosa E, Borght TV, Moreno E. Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study. Mov Disord. Dec 2007;22(16):2346-2351. PMID 17914722


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<td>10/15/12</td>
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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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