This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

<table>
<thead>
<tr>
<th>Populations</th>
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**DESCRIPTION**

Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), using radiopharmaceutical ioflupane (\(^{123}\) 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 from Alzheimer disease.

**SUMMARY OF EVIDENCE**

For individuals who have clinically uncertain Parkinson disease who receive DaT-SPECT, the evidence includes randomized controlled trials (RCTs), 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 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 the effects of this technology on health outcomes.

For individuals who have clinically uncertain dementia with Lewy bodies who receive DaT-SPECT, the evidence includes RCTs, 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.

**POLICY**

Dopamine transporter imaging with single-photon emission computed tomography is 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.

**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 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 derive 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).1, 2

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.1

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 sup-
ports 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 are a group of diseases that share similar cardinal signs, characterized by bradykinesia, rigidity, resting tremor, and gait disturbance. 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.

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.3 Even in specialized movement disorders centers, up to 25% of patients may be misclassified, and some patients (e.g., those with essential tremor who have been diagnosed with PD) may be erroneously treated.4 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 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.5

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.

**REGULATORY STATUS**

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.”6 U.S. Food Drug Administration product code: KPS.
RELATED PROTOCOL

Deep Brain Stimulation

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


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


