FEP Medical Policy Manual

FEP 6.01.54 Dopamine Transporter Single-Photon Emission Computed Tomography

Effective Policy Date: January 1, 2020

Original Policy Date: December 2012

Related Policies:
6.01.06 - Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography
7.01.63 - Deep Brain Stimulation

Dopamine Transporter Single-Photon Emission Computed Tomography

Description

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 non-parkinsonian tremor, as well as dementia with Lewy bodies (DLB) from Alzheimer disease.

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 123I-2β-carbomethoxy-3β-(4-iodophenyl) tropane (\(^{123}\text{I}-\beta\text{-CIT}\)), which is a cocaine analogue with an affinity for both dopamine and serotonin transporters. Intravenous \(^{123}\text{I}-\beta\text{-CIT}\) requires a delay between injection and scan of about 24 hours. Iodine-123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (\(^{123}\text{I}-\text{FP-CIT}\)) is a fluoropropyl derivate of β-CIT that is selective for brain striatal DaT but can also bind to the serotonin transporter. Intravenous \(^{123}\text{I}-\text{FP-CIT}\) can be injected three to six 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 (\(^{99\text{mTc}}\text{-TRODAT-1}\)).

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Binding of ligands with an affinity for DaT ligands in the striatum is, in general, reduced in Parkinson disease (PD), genetic parkinsonism, DBL, 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 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 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 endpoint, 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.

**OBJECTIVE**

The objective of this evidence review is to determine whether dopamine transporter imaging with single-photon emission computed tomography improves health outcomes in individuals with clinically uncertain Parkinson disease or clinically uncertain dementia with Lewy bodies.

**POLICY STATEMENT**

Dopamine transporter imaging with single-photon emission computed tomography may be considered medically necessary when used for individuals with:

- clinically uncertain Parkinson disease; or
- 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.

**POLICY GUIDELINES**

None

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).
FDA 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."

U.S. Food Drug Administration product code: KPS.

RATIONALE

Summary of Evidence

For individuals who have clinically uncertain Parkinson's 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. The 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 limitations in study design, conduct, and relevance. Evidence on clinical utility in the target population includes a RCT 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 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. 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 (DLB) who receive DaT-SPECT, the published evidence includes RCTs, cohort studies, and case series studies. The 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 DLB. No studies have directly evaluated the effect of DaT-SPECT 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.

SUPPLEMENTAL INFORMATION

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 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 SPECT tracer studies exploring the presynaptic dopamine transporter are appropriate for the differential diagnosis of parkinsonian syndromes. No studies have evaluated the effect of DaT-SPECT on health outcomes in the target population of clinically uncertain PDS.
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 DaT imaging with 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 practice parameters from the American Academy of Neurology (2006; reaffirmed 2013) stated 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, 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 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 MDS (2015) diagnostic criteria for PD are intended for use in clinical research but can be 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.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (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 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 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.

U.S. Preventive Services Task Force Recommendations

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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.

**REFERENCES**


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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

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<th>Date</th>
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<td>December 2012</td>
<td>New policy</td>
<td>Updated policy with literature review. Added reference 19 and 24. No change to policy statement or summary.</td>
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<td>December 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review; reference 6 added; policy statement unchanged.</td>
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<tr>
<td>March 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review; references 33, 35, 39, 41, and 45 added; reference 38 updated. Policy statement unchanged.</td>
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<tr>
<td>December 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 21, 2017; Rationale revised and several references added. Policy statement unchanged.</td>
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<tr>
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<td>Replace policy</td>
<td>Policy updated with literature review through August 4, 2018. Change 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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