Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography

Policy Number: 6.01.54  Last Review: 9/2020
Origination: 9/2015  Next Review: 9/2021

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
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.

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

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<td>Individuals:</td>
<td></td>
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<td>Relevance outcomes include:</td>
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<tr>
<td>• With clinically uncertain Parkinson disease</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>• Symptoms</td>
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<td></td>
<td>• Dopamine transporter single-photon emission</td>
<td>• Standard diagnostic workup without</td>
<td>• Functional outcomes</td>
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<td></td>
<td>computed tomography</td>
<td>dopamine transporter single-photon emission computed tomography</td>
<td>• Treatment-related mortality</td>
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<td>• Treatment-related morbidity</td>
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<td>Individuals:</td>
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<tr>
<td>• With clinically uncertain dementia with</td>
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<td>Lewy bodies</td>
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</table>

Related outcomes include:
- Symptoms
- Functional outcomes
- Treatment-related mortality
- Treatment-related morbidity
Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), using radiopharmaceutical ioflupane (\(^{123}\)I) injection, is a neuroimaging modality being evaluated to improve the differential diagnosis of parkinsonian syndromes from nonparkinsonian tremor, as well as dementia with Lewy bodies from Alzheimer disease.

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 randomized controlled trial 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 Parkinson disease. 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 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.

Thus, the above indications may be considered medically necessary considering the suggestive evidence including clinical input support.

**Background**

**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.

**Diagnosis**
Despite the well-known symptoms of PD, diagnosis is challenging even for experienced clinicians, particularly in the 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. 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. 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**
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. 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 123I-2β-carbomethoxy-3β-(4-iodophenyl) tropane (123I-β-CIT), which is a cocaine analogue with an affinity for both dopamine 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 derivative 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 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 (99mTc-TRODAT-1).3,4

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.3

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.5,6 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.7,8,9,10

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.11 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.\textsuperscript{12} 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{13} Further research may shed light on these cases.

**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."\textsuperscript{14}

**Rationale**

This evidence review was created in August 2012 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through July 17, 2019.

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

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Testing for Clinically Uncertain Parkinson Disease**

**Clinical Context and Test Purpose**

The purpose of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) of individuals with clinically uncertain PD is to
include or exclude the diagnosis of PD in order to guide appropriate management decisions.

The question addressed in this evidence review is: In individuals with clinically uncertain PD, does the use of DaT-SPECT improve the net health outcome?

The following PICO's were used to select literature to inform this review.

**Patients**
The populations of interest include individuals with early- or late-stage uncertainty in the diagnosis of PD (following evaluation by a movement disorder specialist). It would also include patients with a continuing diagnostic dilemma of PD vs essential tremor, drug-induced parkinsonism, or vascular parkinsonism.

**Interventions**
The relevant intervention of interest is DaT-SPECT, used as a diagnostic adjunct to the physical exam of patients and review of their medical history.

**Comparators**
The criterion standard for the diagnosis of PD is postmortem neuropathologic examination. In the absence of a criterion standard, clinical evaluation by general neurologists or expert clinicians and observation over time may be used as an interim reference standard endpoint for the diagnosis of PD. The accuracy of PD diagnosis is affected by clinician expertise and the duration of symptoms. While patients may be initially referred to a general neurologist, there is a statistically significant difference in diagnostic specificity between a generalist and a movement disorder specialist. The criterion setting is a tertiary clinic of neurologists specializing in movement disorders (including PD).

**Outcomes**
Health outcomes are defined as disease-related morbidity, functional outcomes, and treatment-related mortality and morbidity. There is a range of assessments for PD-related morbidity, including the 39-item Parkinson Disease Questionnaire, Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale, and Hoehn & Yahr staging system, which may be used to quantify health outcomes. These assessments catalog motor symptoms (ie, tremor, slowness of movements, rigidity, instability), nonmotor symptoms (eg, mood, fatigue, daytime sleepiness), and quality of life (eg, limitations in daily activities due to symptoms). Outcomes may also include treatment-related morbidity and mortality, particularly in regards to the use of dopaminergic medications. With the criterion standard of PD (histopathology), diagnostic accuracy can only be confirmed after death. The reference standard of PD (clinical diagnosis over time) varies both by the degree of clinician expertise and the duration of symptoms prior to evaluation by DaT-SPECT. An estimated mean of 10 years (range, 3.6-13.8 years) is useful for improving clinical diagnostic accuracy.
Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Study Selection Criteria
For the evaluation of clinical validity of striatal dopamine transporter binding imaging, methodologically credible studies were selected using the following principles:

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The most informative evaluation of diagnostic performance requires prospective, independent, and blinded assessment of test results compared with a criterion standard in an appropriate population. There are no such studies assessing DaT-SPECT in patients with clinically uncertain PD (see Tables 1-4).

Studies of clinical validity for DaT-SPECT in diagnosing PD rely on the reference standard endpoint of diagnosis by a clinician, based on physical diagnosis and patient history.

Systematic Reviews
A meta-analysis of physician diagnosis of PD, relative to histopathology, was published in Rizzo et al (2016).\textsuperscript{15} Clinical diagnosis of PD by expert clinicians had a sensitivity of 81.3% and a specificity of 83%, as assessed by criterion standards (histopathology). Notably, clinical diagnosis by general neurologists had a sensitivity of 89.7% and a specificity of 49.2%, as assessed by criterion standards (histopathology) or reference standards (diagnosis by experts). The accuracy of clinical diagnosis was also relative to the duration of symptoms. The positive predictive value was listed as 26% in a study examining the disease duration of fewer than 3 years, and 53% for disease duration of fewer than 5 years.
Retrospective Studies

Marshall et al (2009) reported on a prospective, investigator-initiated, 3-year European multicenter study of 99 diagnostically uncertain cases of PD or essential tremor (ET). Patients with other potential causes of parkinsonism or tremor and patients with major comorbid illness were excluded; three healthy volunteers were included. DaT-SPECT scans at baseline, 18 months, and 36 months were reported by masked nuclear physicians, using visual analysis with high interreader agreement (κ range, 0.94-0.97). The baseline clinical diagnosis and reference standard endpoint was video analysis of the patient, at the start of the study and after 36 months, by movement disorder specialists who were blinded to imaging data and patient history. Comparison of the baseline DaT-SPECT scans with the reference standard endpoint revealed a sensitivity of 78% and specificity of 97%. Comparison of the baseline clinical diagnosis with the reference standard endpoint showed a sensitivity of 93% and specificity of 46%. Of the 71 patients with clinical diagnosis of parkinsonian syndrome (including PD, multiple system atrophy, and progressive supranuclear palsy) at the end of this study, 1 patient had a DaT-SPECT scan that changed from normal to abnormal between the baseline and the scan at 36 months, and 1 patient had a DaT-SPECT scan that changed from abnormal to normal at the same time. Both patients were clinically diagnosed with PD. Of note, 15 (21%) patients with a clinical diagnosis of PD had unexpectedly normal DaT-SPECT imaging at baseline, 18 months, and 36 months. It is not known whether these cases of scans without evidence of dopaminergic deficit resulted from a false-negative DaT-SPECT scan or an incorrect reference standard endpoint of clinical diagnosis. Strengths and weaknesses of this study are detailed in Tables 1, 3, and 4.

A number of studies were excluded from further review for the absence of an independent reference standard endpoint because it was not clear that clinicians were blinded to DaT-SPECT results (see Table 3). Vlaar et al (2008) retrospectively reviewed a population of patients with clinically uncertain PD but the reference standard endpoint did not use clinicians blinded to DaT-SPECT scans. Publications by Kupsch et al (2012, 2013), Hauser et al (2014), and Bajaj et al (2014) derive from a common data set on clinically uncertain parkinsonian syndrome (including PD, multiple system atrophy, and progressive supranuclear palsy), which did not use clinicians blinded to DaT-SPECT scans. Further strengths and weaknesses in study designs and analyses for these studies are detailed in Tables 1, 3, and 4. Three of 5 studies in a meta-analysis by Brigo et al (2014) did not use clinicians blinded to DaT-SPECT scans. One of 4 studies in the meta-analysis by O'Brien et al (2014) did not use clinicians blinded to DaT-SPECT scans. When a reference standard is not independent of the diagnostic test, it can result in an apparent increase in the sensitivity and specificity of the test. Therefore, the diagnostic accuracy reported in these studies must be interpreted cautiously.
Table 1. Clinical Validity Study Selection

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Selection Criteria</th>
<th>Exclusion Criteria</th>
<th>Drop-Outs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vlaar et al (2008)</td>
<td>1 European site</td>
<td>Referral by neurologist</td>
<td>• Clear, unequivocal diagnosis prior to ordering DaT-SPECT scan</td>
<td>• Final diagnosis unclear • Different test performed</td>
</tr>
<tr>
<td>Marshall et al (2009)</td>
<td>10 European sites</td>
<td>• Clinically uncertain PD • Met criteria for both PS and ET • UPDRS-III score ≤16</td>
<td>• Other potential causes of parkinsonism or tremor • Major comorbid illness • Iodine sensitivity • Protocol violations • Personal reasons • Safety or medical reasons • Loss to follow-up</td>
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</tr>
<tr>
<td>Kupsch et al (2012, 2013)</td>
<td>19 U.S. and European centers</td>
<td>• Clinically uncertain, monosymptomatic, atypical, or incomplete presentation with possible parkinsonian syndrome • Early-onset parkinsonian syndrome (&lt;5 y of symptoms)</td>
<td>• Differential diagnosis of PD vs PSP or MSA • Diagnosed movement disorder or cause of tremor • Significant cognitive impairment • Medications known to interact with DaT-SPECT scan</td>
<td>• Protocol violations • Patient request • Loss to follow-up</td>
</tr>
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Table 2. Clinical Validity Study Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Scenario (N)</th>
<th>OR</th>
<th>Sensitivity (95% CI), %; p</th>
<th>Specificity (95% CI), %; p</th>
<th>PPV (95% CI), %</th>
<th>NPV (95% CI), %</th>
</tr>
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<tbody>
<tr>
<td>Vlaar et al (2008)</td>
<td>PD (127) vs ET (22)</td>
<td>82 61</td>
<td>80 80 80 80 80</td>
<td>95 80 100 80 24</td>
<td>99 100 100 87 15</td>
<td>48 39 15 15</td>
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<td>PD (127) vs VP (16)</td>
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<td></td>
<td>PD (127) vs DIP (5)</td>
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<tr>
<td></td>
<td>PD (127) vs APS (27)</td>
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<td></td>
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<tr>
<td>Marshall et al (2009)</td>
<td>PS (71) vs non-PS (28)</td>
<td>NR</td>
<td>78.0 (66.0 to 87.5) &lt;0.001</td>
<td>96.8 (83.3 to 99.9) 0.002</td>
<td>98.2 (90.1 to 100) NR</td>
<td>66.2 (49.8 to 80.0) NR</td>
</tr>
<tr>
<td>Kupsch et al (2012, 2013)</td>
<td>PS (42) vs ET (17)</td>
<td>NR</td>
<td>95.2 (83.8 to 99.4) 100</td>
<td>100 (80.5 to 100)</td>
<td>100 (91.2 to 100) 89.5</td>
<td>89.5 (66.9 to 98.7)</td>
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<tr>
<td></td>
<td>Hauser et al (2014)</td>
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</table>
APS: atypical parkinsonian syndromes; CI: confidence interval; DIP: drug-induced parkinsonism; ET: essential tremor; NPV: negative predictive value; NR: not reported; OR: odds ratio; PD: Parkinson disease; PPV: positive predictive value; PS: parkinsonian syndromes including PD, multiple system atrophy, and progressive supranuclear palsy; VP: vascular parkinsonism.

a Only data on the 123I-Ioflupane dopamine transporter imaging are reported here; results from the iodine 123 iodobenzamide tracer were disregarded.

Table 3. Clinical Validity Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Duration of FUe</th>
</tr>
</thead>
</table>
2. Clinical history sufficient for diagnosis in 154/248 patients
2. 61/248 patients had parkinsonism as only differential diagnosis | 2. Unclear criteria for assigning patients for DaT-SPECT by tracers for dopamine transporters and/or receptors | 2. Clinical diagnosis performed by both residents and movement specialists
2. Physicians not consistently blinded to DaT-SPECT results | 1. No health outcomes reported
2. No clinical decisions described
3. No evidence chain explicated
5. No AEs discussed | 1. Insufficient follow-up between initial and final clinical diagnoses to improve clinical accuracy
1. Not all patients had a final diagnosis |
| Marshall et al (2009)17       | 3. Patients met criteria for both PS and ET; excludes other causes of parkinsonism |  | 1. No health outcomes reported
2. No clinical decisions described
5. No AEs discussed |  |  |
2. Physicians not blinded to DaT-SPECT results |  | 1. Insufficient follow-up between initial and final clinical diagnoses to improve clinical accuracy
1. Not all patients had a final diagnosis |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

AE: adverse event; DaT-SPECT: dopamine transporter imaging with single-photon emission computed tomography; ET: essential tremor; FU: follow-up; PS: parkinsonian syndromes including Parkinson disease, multiple system atrophy, and progressive supranuclear palsy.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 4. Clinical Validity Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Selectiona</th>
<th>Blindingb</th>
<th>Delivery of Testc</th>
<th>Selective Reportingd</th>
<th>Data Completenesse</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vlaar et al (2008)18</td>
<td>1. Selection not described</td>
<td>1. Final clinical diagnosis not consistently blinded to scan results</td>
<td>3. Unclear if quantitative, visual, or combined analysis used to interpret scans</td>
<td>1. Unclear what percentage of patients undergoing 123I-Iofluopane scan were excluded after enrollment</td>
<td>1. Variable FU pathways; did not always include direct patient exam or interaction</td>
<td></td>
</tr>
<tr>
<td>Marshall et al (2009)17</td>
<td>1. Selection not described</td>
<td>1. DaT-SPECT analysis not consistently blinded</td>
<td>1. Clinical endpoint not blinded (per study design)</td>
<td>2. 100 (50%) of 199 patients excluded after enrollment</td>
<td>2. 43 (32%) of 135 patients assigned to receive DaT-SPECT excluded after enrollment</td>
<td>1. Some p values not reported</td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

DAT-SPECT: dopamine transporter imaging with single-photon emission computed tomography; FU: follow-up.

a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

b Blinding key: 1. Not blinded to results of reference or other comparator tests.

c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.


e Follow-Up key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.
Section Summary: Clinically Valid
A meta-analysis of postmortem histopathology studies established an expert clinical diagnosis as a reference standard with high sensitivity and low-to-moderate specificity. Studies using this reference standard are limited by limitations in study designs, conduct, and relevance. Specific areas of concern include unclear study populations, missing data, insufficient follow-up, and inconsistent blinding. The diagnostic accuracy of DaT-SPECT cannot be determined from these studies. Evidence reported through clinical input augments the published evidence by reporting that DaT-SPECT provides clinically meaningful improvement for detecting nigrostriatal degeneration and improved accuracy compared with standard diagnostic workup with the physical diagnosis alone. In addition, other DaT-SPECT tracers (eg, iodine 123I-2β-carbomethoxy-3β-(4-iodophenyl) tropane[^123I-β-CIT]) have supporting studies that used histopathologic confirmation to demonstrate DaT-SPECT's ability to accurately detect the presence of nigrostriatal degeneration. These data along with other studies showing similar diagnostic performance comparing SPECT using 123I-β-CIT tracer vs Iodine-123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (or 123I-lofupane; DaTscan) provide supportive evidence for the clinical validity of DaT-SPECT. Further details from clinical input are included in the Clinical Input section and the Appendix.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

The preferred RCT would evaluate health outcomes in patients with clinically uncertain PD who received the new diagnostic test compared with patients who received standard of care. For the purposes of this trial, health outcomes are defined as disease-related symptoms, functional outcomes, and treatment-related mortality and morbidity. Physician confidence, changes in diagnosis, and changes in management were not sufficient to consider independently as health outcomes.

Kupsch et al (2012, 2013) reported on an open-label, multicenter randomized trial from 19 university hospital centers in Europe and the U. S.[^19,20]. This reporting drew from a common data set on clinically uncertain parkinsonian syndrome (including PD, multiple system atrophy, and progressive supranuclear palsy), which was discussed previously and reviewed in Tables 1 through 4[^19,20,21,22]. Patients were randomized to DaT-SPECT (n=109) or no imaging (n=123), with DaT-SPECT scans classified as normal or abnormal by a physician.
blinded to clinical history; they were then followed for 1 year by neurologists with (n=12) or without (n=7) movement disorder specialization. Health outcomes at three months after a scan revealed no significant difference in the quality of life.20. Again, health outcomes in the same population at one year after the scan showed no significant differences in the quality of life or health resource utilization between those who received a DaT-SPECT scan and those who did not.19.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence demonstrating that DaT-SPECT results improve health outcomes would require that improved diagnostic performance (NPV, PPV) of the DaT-SPECT test, relative to the reference standard, resulted in specific management changes that have been shown to improve health outcomes. Changes in medications alone are not sufficient to demonstrate improved health outcomes unless these changes are demonstrated to be applied correctly and beneficially in the target population.

Case Series
Sadasivan and Friedman (2015) reported on a case series of patients with the clinically uncertain parkinsonian syndrome (n=65), including PD, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration, who were referred for DaT-SPECT over a 17-month period.25. Scans were abnormal in 22 patients given a final diagnosis of parkinsonian syndrome. Change in clinical management was seen in 41 (63%) patients, of whom 30 (73%) were either clinically stable or improved at follow-up. A subset of ten patients was found to have drug-induced PD without any striatal neurodegeneration noted on the DaT-SPECT scan; these patients were then advised to discontinue the drugs or reduce the doses of their drug intake. No follow-up information comparing DaT-SPECT with the reference standard (clinical diagnosis over sufficient time), which would validate treatment decisions, was provided. Specific health outcomes resulting from a specific change in management were also not provided.

Oravivattanakul et al (2015) reported on a case series of patients with baseline diagnoses of neurodegenerative parkinsonism (including PD, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration; n=70), non-neurodegenerative parkinsonism (n=46), uncertain diagnosis (n=45), and ET (n=14).26. All but 3 of the 78 patients with abnormal DaT-SPECT scans were started or continued on medications. Of the 95 patients with normal DaT-SPECT scans, 23 patients were started or continued on medications. Drug management for patients with indeterminate DaT-SPECT scans (n=2) was not discussed. Study weaknesses included the small sample size with uncertain diagnosis and uncertain duration of clinical follow-up.

Bega et al (2015) reported on a case series of 83 patients with clinically uncertain PD who received DaT-SPECT.27. Patients were classified by diagnostic dilemma,
including PD vs ET (n=18), PD vs drug-induced parkinsonism (n=18), or PD vs vascular parkinsonism (n=12). While the series detailed initiation, discontinuation, or escalation of medications for PD in these subpopulations, these changes in management were not linked to specific diagnostic decisions or DaT-SPECT results.

Several studies were excluded from this review because they lacked appropriate health outcome metrics, as described above. Two of them reviewed a prospective multicenter trial on the diagnostic and clinical management impact of DaT-SPECT on 118 patients with clinically uncertain parkinsonism syndrome; while imaging changed diagnosis and management, neither study detailed these outcomes relative to specific diagnostic changes.

Section Summary: Clinically Useful
Evidence on clinical utility includes an RCT and several case series that have evaluated the effect of DaT-SPECT on diagnosis and changes in treatment. The RCT revealed that patients evaluated using DaT-SPECT had no improvement in health outcomes, when compared with those not evaluated using DaT-SPECT, at the three-month and one-year follow-up period. Several case series studies have documented a change in diagnosis and management but did not comment on health outcomes. One case series evaluating neurodegenerative parkinsonian syndromes, including PD, indicated that changes based on imaging scans resulted in stable or improved health outcomes, but lacked an appropriate reference standard to evaluate whether changes were made in the direction of more accurate diagnosis and more appropriate management. Therefore, a chain of evidence linking DaT-SPECT to improved patient outcome cannot be constructed. Evidence reported through clinical input augments the published evidence by outlining a chain of evidence how the use of DaT-SPECT informs management decisions that improve the net health outcome of care. For individuals with clinically uncertain PD, which includes unusual clinical features, incomplete or uncertain responsiveness to dopaminergic medication, or clinical diagnostic uncertainty after evaluation by a specialist, negative results on DaT-SPECT may be used to distinguish neurodegenerative parkinsonian syndromes involving functional loss of dopamine system (eg, PD; progressive supranuclear palsy; corticobasal degeneration; multiple system atrophy; dementia with Lewy bodies) from conditions without functional loss of dopamine system (eg, essential tremor, drug-induced parkinsonism, or vascular parkinsonism). Use of DaT-SPECT to exclude functional loss of the dopamine system (ie, nigrostriatal degeneration) may be clinically useful to inform treatment decisions by reducing or avoiding unnecessary dopaminergic therapy. With regard to the RCT comparing health outcomes at one year, clinical input provided additional context that one-year follow-up may be too short to identify significant changes in quality of life in a slowly progressive condition such as PD. Further details from clinical input are included in the Clinical Input section and the Appendix.

Testing for Clinically Uncertain Dementia With Lewy Bodies
**Clinical Context and Test Purpose**
The purpose of DaT-SPECT testing of individuals with uncertain DLB is to establish the clinical diagnosis of DLB in order to guide appropriate management decisions.

The question addressed in this evidence review is: In individuals with uncertain DLB, does the use of DaT-SPECT testing improve the net health outcome?

The following PICOs were used to select literature to inform this review.

**Patients**
The populations of interest include individuals with an uncertain diagnosis of DLB after assessment by a specialist in dementia disorders. The population would also include patients with an ongoing diagnostic dilemma of DLB vs Alzheimer disease.

**Interventions**
The relevant intervention of interest is DaT-SPECT, used as a diagnostic adjunct to a physical exam and medical history.

**Comparators**
The criterion standard for the diagnosis of DLB is postmortem neuropathologic examination. In the absence of comparisons with the criterion standard, diagnosis by expert clinicians may be used as a reference standard for diagnosis of DLB. The criterion setting is a dementia specialist practice for patients undergoing evaluation for DLB and other dementia.

**Outcomes**
Health outcomes are defined as disease-related morbidity, functional outcomes, and treatment-related mortality and morbidity. Assessment of DLB may include tests such as the Lewy Body Composite Risk Score, which assesses motor symptoms (ie, rigidity, postural instability) and non-motor symptoms (ie, daytime sleepiness, hallucinations). Assessment of DLB may also include general tests for dementia including the Clinical Dementia Rating test. With the criterion standard of DLB (histopathology), diagnostic accuracy can only be confirmed after death. The reference standard of DLB is a clinical diagnosis.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Study Selection Criteria**
For the evaluation of clinical validity of striatal dopamine transporter binding imaging, methodologically credible studies were selected using the following principles:
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The most informative evaluation of diagnostic performance requires prospective, independent, and blinded assessment of test results compared with a criterion standard in an appropriate population. There are no such studies for DaT-SPECT in patients with clinically uncertain DLB.

The largest study to evaluate DaT-SPECT for DLB is the prospective, investigator-initiated, multicenter study by McKeith et al (2007). It reviewed 326 patients with a clinical diagnosis of probable (n=94) or possible (n=57) DLB or non-DLB (n=147). Baseline diagnoses were established by a consensus panel of 3 clinicians without access to DaT-SPECT results; a diagnosis could not be made in 28 patients. DaT-SPECT scans were assessed visually by three nuclear medicine physicians with expertise in DaT-SPECT who were unaware of the clinical diagnosis. DaT-SPECT had a mean sensitivity of 77.7% for detecting clinically probable DLB, a mean specificity of 90.4% for excluding non-DLB dementia, a PPV of 82.4%, and an NPV of 87.5%. This phase 3 study did not use long-term clinical follow-up as the standard.

**Section Summary: Clinically Valid**
Published evidence on clinical validity includes the limited duration of long-term clinical follow-up to confirm the diagnosis. Evidence reported through clinical input augments the published evidence by highlighting that DaT-SPECT helps to confirm when individuals with DLB may have nigrostriatal degeneration; whereas individuals with typical Alzheimer-type dementia would not be expected to have a functional loss of the dopamine system. As noted in the indication for clinically uncertain PD, DaT-SPECT provides clinically valid detection of nigrostriatal degeneration and improved accuracy compared with standard diagnostic workup with the physical diagnosis alone in the Parkinsonian syndrome population and would be expected to provide clinically valid results for identifying functional loss of dopamine system in DLB. Further details from clinical input included in the Clinical Input section and the Appendix.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be
improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

The preferred RCT would evaluate health outcomes in patients with clinically uncertain DLB who received the new diagnostic test compared with patients who received the standard of care. Physician confidence, changes in diagnosis, and changes in management alone would not be sufficient to consider independently as health outcomes. Changes in management decisions were accepted as the reference standard only if the authors linked changes in medications to specific diagnostic changes made as a result of DaT-SPECT.

Several studies were excluded from this review because they lacked appropriate health outcome metrics. An RCT by Walker et al (2015) reviewed the diagnostic change and diagnostic confidence alone, which was not considered meaningful health outcomes for this evidence review.\(^\text{32}\) Reanalysis of the same data set by Walker et al (2016) focused on correlating symptoms with DaT-SPECT results and was discounted because it falls outside the scope of this review of DaT-SPECT as a diagnostic tool.\(^\text{33}\) Both studies were limited by a small population (n=114) and short follow-up (6 months). Finally, Kemp et al (2011) retrospectively evaluated 80 consecutive patients with DLB; while imaging affected patient management, these outcomes were not detailed with respect to specific diagnostic changes.\(^\text{34}\) Further, many (irrespective of the imaging results) were in the earliest phase of their disease process and did not require immediate treatment for symptoms.

**Chain of Evidence**
Indirect evidence on clinical utility may use a chain of evidence linking the use of the results to inform management decisions that improve the net health outcome of care. Published evidence does not demonstrate a chain of evidence.

**Section Summary: Clinically Useful**
No studies on the impact of DaT-SPECT imaging on clinical outcomes have been published. Evidence reported through clinical input augments the published evidence by outlining how the use of DaT-SPECT informs management decisions that improve the net health outcome of care. For individuals with clinically uncertain DLB, which includes individuals with signs of dementia and suggestion of parkinsonism (eg, motor abnormalities) or early hallucinations, positive results on DaT-SPECT may be used to distinguish possible DLB from Alzheimer disease. Use of DaT-SPECT to confirm the functional loss of the dopamine system and suspected DLB may be clinically useful to inform treatment decisions by avoiding the potentially harmful effects of neuroleptics typically used in dementia patients. Further details from clinical input included in the Clinical Input section and the Appendix.
CLINICAL INPUT

Objective
In 2018, clinical input was sought to help determine whether the use of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) in individuals with clinically uncertain Parkinson disease or clinically uncertain dementia with Lewy bodies and would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

Respondents
Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Society of Nuclear Medicine and Molecular Imaging
- Anonymous, MD, Neurology, Movement Disorders, identified by American Academy of Neurology (AAN)
- Jacob G. Dubroff, MD, PhD, Nuclear Medicine, Assistant Professor of Radiology, University of Pennsylvania, identified by American College of Radiology (ACR)\(^a\)

\(^a\) Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide a review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA nor any Blue Plan.

Clinical Input Responses
Figure 1:

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<th>Clinical Indication</th>
<th>Respondent</th>
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<td>AAN</td>
</tr>
<tr>
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<td>AAN</td>
</tr>
<tr>
<td></td>
<td>Dr. Dubreft*</td>
<td>ACR</td>
</tr>
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<td>Use of DaTSPECT for individuals with clinically uncertain dementia with Lewy bodies</td>
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<td></td>
<td>Dr. Dubreft*</td>
<td>ACR</td>
</tr>
</tbody>
</table>


* Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Additional Comments

- "The DaTSPECT (DAT) scan test should not be considered a test for Parkinson's disease (PD). It is a test which effectively assesses the functional involvement of the striatal dopamine system. As such, the test, most effectively tests whether the dopamine system has been affected or not. The test should only be used after a neurologist has established the clinical possibility (differential diagnosis) of any one of the neurodegenerative syndromes (PD [Parkinson disease], PSP [progressive supranuclear palsy], CBD [corticobasal degeneration], DLB [dementia with Lewy bodies], and others) with a differential diagnoses being a nonneurodegenerative syndrome (drug-induced parkinsonism, vascular parkinsonism, essential tremor). The practical clinical utility of the test is that, if normal, the result effectively makes it highly unlikely that any of the neurodegenerative set of diagnoses are present. In clinical practice, the negative DAT scan can change management by indicating a reduction in intensity of empiric dopaminergic medication use and relieve significant anxiety over the possibility of a neurodegenerative syndrome (which can be speculated to reduce health care utilization or phone calls/patient visits to multiple physicians in that subpopulation of patients). While the chain of evidence being sought is not definitive, there is clear evidence that appropriate selection of DAT scanning for uncertain syndromes (particularly distinguishing drug-induced vs vascular parkinsonism as in Bega et al 2015) can change clinical management. There is the Kupsch 2012 study looking at health outcomes which had its flaws as in the review provided. In the absence of definitely health outcomes and gold standard diagnostics, change in clinical management should be taken into consideration -- especially when, in neurology, there is no shortage of selected patients for which either anxiety over diagnosis is driving phone calls or patients who are invested in a clinical PD diagnosis who are taking medications with potential for side-effects. In these cases, the utility of a negative DAT scan can provide
immense benefit to patient-care and justifiable support for the physician to actively work to reduce medication risks." (Anonymous, Neurology, Movement Disorders, identified by AAN)

- "For patients who do not have PD but are concerned about PD (and generate a lot of patient visits, phone calls, anxiety), the DAT scan is an essential clinically appropriate test to assess the dopaminergic system. When normal, it allows a confirmation that they do not have PD (or other neurodegenerative diagnoses that affects the dopamine system), and clarifies appropriate treatment which involves reduction of or cautious use of PD treatments if at all. This is the primary clinical indication I find most helpful." (Anonymous, Neurology, Movement Disorders, identified by AAN)

- "Clinically meaningful outcome can be interpreted in several ways. First, using appropriate agents earlier on in the disease course to support a higher quality of life (e.g. dopaminergic therapy including L-Dopa, dopamine agonists like pramipexole, MAO-B inhibitors like selegiline, anticholinergics like benzotropine, and amantadine). Second, avoiding other medications that could exacerbate dopaminergic loss (e.g. antipsychotics) or removing medications (Drug Induced Parkinsonism) which could be causing the observed symptoms (PMID 15889951). Finally, the benefit of diagnostic confidence is under-valued and under-explored as optimizing the ability of a patient and family to plan and anticipate the course this disease is implicit in light of its mean 8-10 year survival from the time of diagnosis (PMID 18362281, 19224612). That is, having greater diagnostic certainty and knowing sooner help both doctor and patient (including families) best manage this devastating disease better." (Dr. Dubroff, Nuclear Medicine, identified by ACR)

- "The main use for DAT scans in clinically uncertain DLB in dementia clinics is the identification of patients with early hallucinations for whom a neuroleptic treatment is being considered. In most cases of early dementia, if there is a typical AD (Alzheimer's) type dementia with no red flags of early hallucinations or soft parkinsonism signs, neuroleptics are often used and escalated in potency. However, when there are some suggestions of parkinsonism or early hallucinations (criteria to consider DLB), the key consideration is whether a DAT scan can be used to highlight the distinction between those who should not receive neuroleptics (DLB) vs those who often do receive neuroleptics (AD). In clinically uncertain DLB, if the decision to escalate or use neuroleptics that are more risky (i.e. atypicals such as quetiapine are not helpful), a DAT scan may be used to ensure that empiric use of a more typical (and potent) neuroleptic is not given to a DLB patient with devastating consequences. In practice, the issue is that neuroleptics are often empirically used and escalated in dementia patients. If an excessive (and sometimes fatal) neuroleptic reaction occurs, the retrospective diagnosis of DLB is made, and only after excessive health care costs of hospitalization may have been incurred. The empiric and ideal study that would study if DAT scan can identify patients before such patients receive neuroleptics beyond quetiapine has not yet been done." (Anonymous, Neurology, Movement Disorders, identified by AAN)
See Appendix 1 and 2 for details.

**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 PD 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. 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 an 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 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**
Clinical Input From Physician Specialty Societies and Academic Medical Centers
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 (PD) and clinically uncertain dementia with Lewy bodies (DLB) 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;
- Use of DaT-SPECT for individuals with clinically uncertain dementia with Lewy bodies.

Practice Guidelines and Position Statements

American College of Radiology
The American College of Radiology (2015) published appropriateness criteria for dementia and movement disorders.35 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 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).36 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.37 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.\(^{38}\) 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.\(^{39}\)

**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,\(^ {40}\) which was updated in 2017.\(^ {41,42}\) The 2006 guidance stated that iodine 123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (\(^{123}\)I-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 \(^{123}\)I-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.\(^ {43}\) It recommended that \(^{123}\)I-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.\(^ {44}\) 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 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**
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.

**Ongoing and Unpublished Clinical Trials**
Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

**Table 5. Summary of Key Trials**

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NCT: national clinical trial.

**REFERENCES**


**Billing Coding/Physician Documentation Information**

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**ICD-10 Codes**

- **G20**: Parkinson's disease (includes primary parkinsonism)
- **G21.0-**: Secondary parkinsonism code range
- **G21.9**:
G31.83  Dementia with Lewy bodies

**Additional Policy Key Words**
N/A

**Policy Implementation/Update Information**

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**APPENDIX 1. CLINICAL INPUT RESPONSES**

**Appendix Table 1. Respondent Profile**

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**Physician**

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**Identified by American College of Radiology**

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<tr>
<td>3</td>
<td>Jacob G. Dubrof</td>
<td>MD, PhD</td>
<td>Assistant Professor of Radiology, University of Pennsylvania</td>
<td>Nuclear medicine</td>
<td>American Board of Nuclear Medicine</td>
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**Appendix Table 2. Respondent Conflict of Interest Disclosure**

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<tr>
<th>No</th>
<th>1. Research support related to the topic where clinical input is</th>
<th>2. Positions, paid or unpaid, related to the topic where clinical input is</th>
<th>3. Reportable, more than $1000, health care–related</th>
<th>4. Reportable, more than $350, gifts or travel reimbursements for</th>
</tr>
</thead>
</table>
Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.

**APPENDIX 2. CLINICAL INPUT RESPONSES**

**Objective**
Clinical input is sought to help determine whether the use of a particular technology for a population would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. We are particularly interested to identify if there are clinical scenarios (population and indication) where a reliable clinical result would be clearly linked to a corresponding management action that is expected to provide a clinically meaningful improvement in net health outcome.

The following PICO applies to this indication.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest</td>
<td>Comparators of interest</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With clinically uncertain Parkinson disease</td>
<td>• Dopamine transporter single-photon emission computed tomography</td>
<td>• Standard diagnostic workup without dopamine transporter single-photon emission computed tomography</td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
</tbody>
</table>

Individuals:

Interventions of interest are:
• Dopamine transporter single-photon emission computed tomography

Comparators of interest are:
• Standard diagnostic workup without dopamine transporter single-photon emission computed tomography

Relevant outcomes include:
• Symptoms
• Functional outcomes
• Treatment-related mortality
• Treatment-related morbidity
Responses
1. Based on the evidence and your clinical experience, describe for each clinical indication listed below the narrative rationale that includes: (1) relevant authoritative scientific evidence and/or relevant clinical scenarios (e.g., a chain of evidence) supporting that use of the technology provides clinical meaningful improvement in net health outcome; and (2) any relevant patient inclusion or exclusion criteria or clinical context important to achieve a clinically meaningful improvement in net health outcome. Please include the PMID for any relevant references.

a. Use of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) for individuals with clinically uncertain Parkinson disease (PD).

Rationale
1 DAT SPECT imaging using 123I-FP-CIT SPECT (or 123I-ioflupane; DaTSCAN) is a very sensitive imaging technique to detect nigrostriatal degeneration in PD, even in preclinical phases (e.g., PMID: 28833467). Studies in clinically uncertain parkinsonian syndromes (CUPS) also showed its clinical validity (e.g., PMID: 19117369). Studies that examined the clinical validity of this technique in CUPS used clinical follow-up data as the reference test. In the literature on clinical validity of this test, post-mortem histopathology correlation is rarely used. However, other DAT SPECT tracers, and particularly 123I-beta-CIT (comparable to FCIT also from a chemical point of view) used this approach (e.g., PMID: 25048738). Since head-to-head studies showed comparable results between both tracers (i.e., same accuracy to detect loss of striatal DAT binding; e.g., PMID: 9044880), data of beta-CIT SPECT studies may be relevant to take also into account when addressing the clinical validity and utility of 123I-FP-CIT SPECT. In this regard, studies on SWEDD performed with beta-CIT SPECT may be of relevance to predict the accuracy of 123I-FP-CIT SPECT on this topic (e.g., PMID: 24759846). Nevertheless, there is need for more studies in SWEDD, as well as studies in CUPS with post-mortem confirmation. References


2 The DaTSPECT (DAT) scan test should not be considered a test for Parkinson’s disease (PD). It is a test which effectively assesses the functional involvement of the striatal dopamine system. As such, the test, most effectively tests whether the dopamine system has been affected or not. The test should only be used Original Review Date: August 2012 Page: 26 © 2018 Blue Cross Blue Shield Association. Reproduction without prior authorization is prohibited. MPRM 6.01.54 Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography after a neurologist has established the clinical possibility (differential diagnosis) of any one of the neurodegenerative syndromes (PD, PSP, CBD, DLB, and others) with a differential diagnoses being a nonneurodegenerative syndrome (drug-induced parkinsonism, vascular parkinsonism, essential tremor). The practical clinical utility of the test is that, if normal, the result effectively makes it
highly unlikely that any of the neurodegenerative set of diagnoses are present. In clinical practice, the negative DAT scan can change management by indicating a reduction in intensity of empiric dopaminergic medication use and relieve significant anxiety over the possibility of a neurodegenerative syndrome (which can be speculated to reduce health care utilization or phone calls/patient visits to multiple physicians in that subpopulation of patients). While the chain of evidence being sought is not definitive, there is clear evidence that appropriate selection of DAT scanning for uncertain syndromes (particularly distinguishing drug induced vs vascular parkinsonism as in Bega et al 2015) can change clinical management. There is the Kupsch 2012 study looking at health outcomes which had its flaws as in the review provided. In the absence of definitely health outcomes and gold standard diagnostics, change in clinical management should be taken into consideration -- especially when, in neurology, there is no shortage of selected patients for which either anxiety over diagnosis is driving phone calls or patients who are invested in a clinical PD diagnosis who are taking medications with potential for side-effects. In these cases, the utility of a negative DAT scan can provide immense benefit to patient-care and justifiable support for the physician to actively work to reduce medication risks.

References


3 PD is a chronic disease that often progresses insidiously, leaving significant diagnostic uncertainty. Therefore, the time-course of clinical meaningful improvement should be carefully considered. I-123 Ioflupane SPECT brain imaging (aka I-123 FP-CIT, DaTscan) is a safe, noninvasive, FDA approved, highly sensitive nuclear medicine imaging technique (PMID24947061) that identifies loss of striatal dopaminergic neurons, a known manifestation of PD, that has consistently demonstrated to have significantly superior accuracy to physical diagnosis alone (PMID 22492213, 19117369). It has shown to be particularly useful in the setting of diagnostic uncertainty (PMID 25592727). Clinically meaningful outcome can be interpreted in several ways. First, using appropriate agents earlier on in the disease course to support a higher quality of life (e.g. dopaminergic therapy including L-Dopa, dopamine agonists like pramipexole, MAO-B inhibitors like selegiline, anticholinergics like benztropine, and amant[a]dine). Second, avoiding other medications that could exacerbate dopaminergic loss (e.g. antipsychotics) or removing medications (Drug Induced Parkinsonism) which could be causing the observed symptoms (PMID 15889951).

Finally, the benefit of diagnostic confidence is under-considered. I-123 Ioflupane SPECT brain imaging (aka I-123 FP-CIT, DaTscan) is a safe, noninvasive, FDA approved, highly sensitive nuclear medicine imaging technique (PMID24947061) that identifies loss of striatal dopaminergic neurons, a known manifestation of PD, that has consistently demonstrated to have significantly superior accuracy to physical diagnosis alone (PMID 22492213, 19117369). It has shown to be particularly useful in the setting of diagnostic uncertainty (PMID 25592727). Clinically meaningful outcome can be interpreted in several ways. First, using appropriate agents earlier on in the disease course to support a higher quality of life (e.g. dopaminergic therapy including L-Dopa, dopamine agonists like pramipexole, MAO-B inhibitors like selegiline, anticholinergics like benztropine, and amant[a]dine). Second, avoiding other medications that could exacerbate dopaminergic loss (e.g. antipsychotics) or removing medications (Drug Induced Parkinsonism) which could be causing the observed symptoms (PMID 15889951).

References


b. Use of DaT-SPECT for individuals with clinically uncertain dementia with Lewy bodies (DLB).

Rationale
1 DLB is the second most common type of dementia, but its diagnosis is challenging due to lack of widespread clinical expertise in making this diagnosis and variable presentation overlapping with PD and other non-parkinsonian syndromes. Behavioral therapies, physical therapy and medications have the greatest benefit if the diagnosis is made early. In addition, therapies targeted for Alzheimer’s diseases, if used for patients with PD, can result in severe and sometimes life-threatening side effects. Therefore, appropriate diagnosis of PD is paramount in avoiding these complications.

2 The main use for DAT scans in clinically uncertain DLB in dementia clinics is the identification of patients with early hallucinations for whom a neuroleptic treatment is being considered. In most cases of early dementia, if there is a typical AD (Alzheimer’s) type dementia with no red flags of early hallucinations or soft parkinsonism signs, neuroleptics are often used and escalated in potency. However, when there are some suggestion of parkinsonism or early hallucinations (criteria to consider DLB), the key consideration is whether a DAT scan can be used to highlight the distinction between those who should not receive neuroleptics (DLB) vs those who often do receive neuroleptics (AD). In clinically uncertain DLB, if the decision to escalate or use neuroleptics that are more risky (i.e. atypicals such as quetiapine are not helpful), a DAT scan may be used to ensure that empir[ic] use of a more typical (and potent) neuroleptic is not given to a DLB patient with devastating consequences. In practice, the issue is that neuroleptics are often empirically used and escalated in dementia patients. If a[n] excessive (and sometimes fatal) neuroleptic reaction occurs, the retrospective diagnosis of DLB is made, and only after excessive health care costs of hospitalization may have been incurred. The empiric and ideal study that would study if DAT scan can identify patients before such patients receive neuroleptics beyond quetiapine has not yet been done.

We note that the review provided comments that “DaT-SPECT has lower sensitivity and higher specificity than expert clinical diagnosis in patients with likely dementia with Lewy bodies.” This statement should be noted that it may be confounded by the fact that diagnoses are often made with the criteria of neuroleptic sensitivity has been demon[strated] already (as part of diagnostic criteria) at which point the clinical utility of a DAT scan is much less, even in patients early in disease process.

3 Like PD, DLB is a chronic progressive disease that can be challenging to diagnose because of its insidious onset. Also similar to PD, there is demise of the of the nigrostriatal dopaminergic brain circuitry for which 1-123 Ioflupane SPECT brain imaging has outstanding sensitivity (PMID 14531044, 16237129, 19300562, 17353255, 25632881). Specifically, DLB’s non-specific cognitive and behavioral symptoms can mimic those also observed in Alzheimer’s disease (AD), the most common neurodegenerative disease. 1-123 Ioflupane SPECT has demonstrated excellent ability to detect the dopaminergic loss seen in DLB in order to distinguish it from AD (PMID 14531044). This is unlike emerging PET amyloid imaging which discern DLB from AD because amyloid is often present in DLB (PMID 25988463). There is also compelling evidence demonstrating that I-123 Ioflupane SPECT brain imaging predicts post-mortem DLB pathology and distinguish it from AD (PMID 27940650, 22961551, 17353255). Mean survival after DLB diagnosis has been estimated to be 8 years (PMID 27725535), similar to PD. This is important as an estimated 50% of DLB patients have a dangerous sensitivity to commonly used neuroleptic drugs including haldol (PMID 16237129). Exposure can often be fatal (PMID 27068351). Thus, avoidance of such medications is of paramount importance.

References

2. Based on the evidence and your clinical experience for each of the clinical indications described in Question 1a and 1b:
   a. Respond Yes or No for each clinical indication whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND
   b. Rate your level of confidence in your Yes or No response using the 1 to 5 scale outlined below.

<table>
<thead>
<tr>
<th>No</th>
<th>Indications</th>
<th>Yes/No</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>1 2</td>
<td>3 4 5</td>
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</tr>
<tr>
<td>1</td>
<td>Use of DaT-SPECT for individuals with clinically uncertain PD</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Use of DaT-SPECT for individuals with clinically uncertain DLB</td>
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</tr>
<tr>
<td>2</td>
<td>Use of DaT-SPECT for individuals with clinically uncertain PD</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Use of DaT-SPECT for individuals with clinically uncertain DLB</td>
<td>Yes</td>
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<tr>
<td>3</td>
<td>Use of DaT-SPECT for individuals with clinically uncertain PD</td>
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</tr>
<tr>
<td></td>
<td>Use of DaT-SPECT for individuals with clinically uncertain DLB</td>
<td>Yes</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

3. Based on the evidence and your clinical experience for each of the clinical indications described in Question 1a and 1b:
a. Respond Yes or No for each clinical indication whether this intervention is consistent with generally accepted medical practice; AND

b. Rate your level of confidence in your Yes or No response using the 1 to 5 scale outlined below.

<table>
<thead>
<tr>
<th>No</th>
<th>Indications</th>
<th>Yes/No</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Use of DaT-SPECT for individuals with clinically uncertain PD</td>
<td>Yes</td>
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<tr>
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<td>Use of DaT-SPECT for individuals with clinically uncertain DLB</td>
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<tr>
<td>3</td>
<td>Use of DaT-SPECT for individuals with clinically uncertain PD</td>
<td>Yes</td>
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<td></td>
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<tr>
<td>4</td>
<td>Use of DaT-SPECT for individuals with clinically uncertain DLB</td>
<td>Yes</td>
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</tbody>
</table>

4. What are the risks and benefits of empirical treatment? (ie, initiating treatment for Parkinson disease [PD] and adjusting, continuing or discontinuing based on treatment response)
   a. For patients who actually have PD?
   b. For patients who do not actually have PD?
   c. Are there any subgroups of patients for whom empirical treatment presents a particular risk?
   d. Are there any subgroups of patients for whom empirical treatment presents a particular benefit?

**Response**

1. Regarding technical utility, without doubt, the intra- and inter-variability for the assessment of 123I-FP-CIT SPECT scans is high (e.g., PMID: 24925885). However, also the test-retest reproducibility of the test itself is high (e.g., PMID: 9829575).

The inclusion criteria, to examine the clinical utility of the tests, are very strict. Following these criteria, indeed, only one RCT examined the relationship between 123I-FP-CIT SPECT and health outcome in CUPS (PMID: 22492213). Although no significant differences in total score for QoL (PDQ-39) or health resource use were observed between groups during the 1-year follow-up period, the authors also described more management changes (including changes in diagnosis) in the imaging arm vs the non-imaging arm. The prognosis of parkinsonian syndromes with degeneration is worse than that for syndromes without degeneration. This is e.g., reflected by the observation that during this study there were 7 hospitalizations in the imaging arm, and all had an abnormal scan. So one may take this also into account when examining the clinical utility. PD is slowly progressive, and when QoL questionnaires like the PDQ-39 are used to measure QoL, longer follow-up data are needed (or larger studies) to show significant changes in relation to DAT imaging. Also, other studies showed that the technique is costeffective (PMID: 18385998; PMID: 18785639). Finally, export reports support the use of 123I-FP-CIT in CUPS (e.g., PMID: 27813429). Therefore, appropriate diagnosis and timely intervention will provide a clinically meaningful improvement in net health outcome of parkinsonian syndromes.

**References**

2
a. For patients who have PD -> empiric tx is standard of care
b. For patients who do not actually have PD, empiric treatment puts patients at risk for side effects of sedation, lightheadedness, hallucinations, vivid dreams, agitation that is not necessary.
c. Patients with atypical parkinsonism carry greater risk for all side effects of empiric treatment with limited benefit.
d. Patients with dystonia (not parkinsonism) are often treated with parkinsonism empirically for which DAT scanning is not indicated and a subgroup (doparesponsive dystonia), the treatment is critical to their well-being.

3 These questions are best answered by Neurologists who sub-specialize in the diagnosis and treatment of movement disorders. However, the risk of using neuroleptic drugs in PD patients is noted (PMID 12735915,15889951).

References

5. What are the risks and benefits of active surveillance, with treatment delayed until presentation is more certain?
a. For patients who actually have PD?
b. For patients who do not actually have PD?
c. Are there any subgroups of patients for whom active surveillance with delayed treatment presents a particular risk?
d. Are there any subgroups of patients for whom active surveillance with delayed treatment presents a particular benefit?

Response
1 We believe that these questions should be answered by movement disorder specialists.
2
a. no issue with empiric follow-up
b. for patients who do not have PD but are concerned about PD (and generate a lot of patient visits, phone calls, anxiety), the DAT scan is an essential clinically appropriate test to assess the dopaminergic system. When normal, it allows a confirmation that they do not have PD (or other neurodegenerative diagnosis that affects the dopamine system), and clarifies appropriate
treatment which involves reduction of or cautious use of PD treatments if at all. This is the primary clinical indication I find most helpful.

c. active follow up for parkinsonism is usually reasonable. If a patient with PD is very against taking PD medications (and perhaps due to denial of diagnosis), in that particular circumstance, when it is clearly clinically indicated to provide treatment of symptoms affecting patient's function or livelihood, a DAT scan, if presented appropriately, can be used address the denial of diagnosis aspect of care. This is not anticipated to come up much at all (has occurred perhaps 1-2 times over 10 years)
d. not particularly.

3 These questions are best answered by Neurologists who sub-specialize in the diagnosis and treatment of movement disorders. However, the risk of using neuroleptic drugs in PD patients is noted (PMID 12735915,15889951).

References

6. How would the availability of an accurate diagnosis of imaging change the balance of risks and benefits in deciding on immediate treatment or surveillance with delayed treatment?
   a. For patients who actually have PD?
   b. For patients who do not actually have PD?

Response
1 We believe that these questions should be answered by movement disorder specialists.
2
   a. decision for treatment for those who have clinical PD is a clinical decision. It does not depend on a DAT scan
   b. decision for treatment for those who do NOT have PD but are being treated for PD is the primary clinical indication for accurate imaging. Accurate imaging reflects state of the dopaminergic system and if normal, it is highly unlikely the patient has a neurodegenerative syndrome such as PD. This will encourage surveillance and holding off on treatment.
3 These questions are also best answered by a Neurology movement disorder specialist.

7. The reference standard we used for the evidence review when evaluating the diagnostic performance of DaT-SPECT for diagnosis of PD is clinical diagnosis by a PD and movement disorder specialist at 3 to 5 years follow-up. This was based on a meta-analysis by Rizzo et al (2016) comparing clinical diagnosis with pathologic findings. Is that the appropriate reference standard? Is there other evidence or rationale for another definition of the reference standard for clinical practice and clinical research? If so, please explain alternative reference standards.

Response
1 We believe that these questions should be answered by movement disorder specialists.
2 No comment.
3 Yes, this is the appropriate reference standard (Rizzo et al. 2016)

8. Additional narrative rationale or comments and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

Additional Comments
1 Both biochemical and imaging biomarkers are increasingly being incorporated into clinical practice. SPECT imaging with DaTScan is a very good example of the biomarker with a great clinical value as it is capable of differentiating non Parkinsonian syndromes which can have similar clinical presentation as Parkinsonian syndromes.
2 No response
3 There are three issues regarding the included evidence summary of I-123 Ioflupane SPECT brain imaging for diagnosis of PD or DLB. First, correlation between I-123 Ioflupane studies and post-mortem tissue as demonstrating the validity of the test are not included (PMID 27940650, 22961551, 17353255). Second, the potential fatal dangers of neuroleptic malignant syndrome in both DLB and PD are under-emphasized (PMID 12735915, 15889951) as poor outcomes that could nearly impossible to evaluate from an ethical perspective using a prospective trial. Finally, in the "Technical Reliability", there is the following uncited statement: "Dopamine agonists and levodopa may also affect DaT expression, which could influence the ability of DaT-SPECT to monitor progression of disease." There is evidence to the CONTRARY (PMID 16151764). Specific medications that bind the molecular target (presynaptic dopamine transporter) of I-123 Ioflupane imaging and could possibly interfere with the study are known and avoided prior to the study (PMID 20019219). This is an great reference that was not included (PMID 24947061).

References

9. Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

<table>
<thead>
<tr>
<th>No.</th>
<th>Yes/No</th>
<th>Citations of Missing Evidence</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>No</td>
<td></td>
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<tr>
<td>2</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>This is summarized in question 8</td>
</tr>
</tbody>
</table>

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.