Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography

Policy # 00496
Original Effective Date: 04/20/2016
Current Effective Date: 01/23/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider dopamine transporter imaging with single-photon emission computed tomography to be eligible for coverage** when used for individuals with:

- Clinically uncertain Parkinson disease following evaluation by a movement disorder specialist, i.e. unusual clinical features, incomplete or uncertain responsiveness to dopaminergic medication, or clinical diagnostic uncertainty; or
- Clinically uncertain dementia with Lewy bodies following evaluation by a specialist in dementia disorders, i.e. individuals with signs of dementia and suggestion of parkinsonism with motor abnormalities, or early hallucinations.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers use of dopamine transporter imaging with single-photon emission computed tomography for all other indications not included above to be investigational.*

Background/Overview

PARKINSON DISEASE
Parkinsonian syndromes are a group of diseases that share similar cardinal signs, characterized by bradykinesia, rigidity, resting tremor, and gait disturbance. Parkinson disease (PD) is the most common cause of parkinsonism.

Diagnosis
Despite the well-known symptoms of PD, diagnosis is challenging even for experienced clinicians, particularly in early stages of the disease. In addition, other etiologies such as essential tremor, corticobasal degeneration, multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism, and drug-induced parkinsonism can lead to a similar set of symptoms.
While the criterion standard is postmortem histopathology, clinical diagnosis may be used as an interim reference standard. The accuracy of the diagnosis is influenced by the duration of the symptoms and the clinician’s experience. Even in specialized movement disorders centers, up to 25% of patients may be misclassified, and some patients (eg, those with essential tremor who have been diagnosed with PD) may be erroneously treated. Such misclassifications have led to the call for additional diagnostic tests and biomarkers to improve the accuracy of clinical diagnosis of PD and other parkinsonian syndromes. One recent approach is to evaluate the integrity of dopaminergic pathways in the brain using dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) imaging.

DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies (DLB) is a type of dementia characterized by parkinsonism, visual hallucinations, cognitive fluctuation, sleep disorders, and severe neuroleptic sensitivity. DLB is the second most common form of degenerative dementia; Alzheimer disease, which can have similar symptoms at onset, is the most common.

Diagnosis

Diagnosis can be challenging, particularly when patients have multiple comorbidities including cerebrovascular disease and/or Alzheimer disease. 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 derivate of β-CIT that is selective for brain striatal DaT but can also bind to the serotonin transporter. Intravenous 123I-FP-CIT can be injected 3 to 6 hours before the scan (DaTscan). Other SPECT ligands with affinity for dopamine transporter include technetium 99m (2β((N,N’-bis(2-mercaptoethyl) ethylene diamino)methyl) and 3β-(4-chlorophenyl) tropane (99mTc-TRODAT-1).

Binding of ligands with affinity for DaT ligands in the striatum is, in general, reduced in PD, genetic parkinsonism, DLB, corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy. In contrast, striatal DaT ligand binding is expected to be within the normal range of Alzheimer disease.
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disease, essential tremor, dystonic tremor, orthostatic tremor, drug-induced parkinsonism, and psychogenic parkinsonism.

Visualization of striatal dopamine transporter binding, through DaT-SPECT, permits assessment of presynaptic dopaminergic deficit. It is proposed that an abnormal DaT-SPECT scan supports the diagnosis of PD, DLB, or other neurodegenerative parkinsonian syndrome, while a normal DaT-SPECT scan in a symptomatic patient supports the diagnosis of a disease not affecting the nigrostriatal dopaminergic pathway.

Analysis of DaT-SPECT images can be visual, semiquantitative, or quantitative. In patients with PD, physical symptoms start after 30% to 50% of dopaminergic neurons have degenerated. Symptomatic patients with PD would be thus expected to have sufficient abnormality on DaT-SPECT for visual analysis to be adequate for interpretation. A variety of methods are being tested to improve the validity and reliability of ratings, including commercially available software to define the region of interest for analysis and the development of an atlas for visual interpretation. Several research centers are developing quantitative and semiquantitative classification methods for the evaluation of DaT-SPECT images.

Anatomic variation in the brain, including vascular lesions, may interfere with the distribution of the iodine-123 tracer and could result in an abnormal scan. Dopamine agonists and levodopa may also affect DaT expression, which could influence the ability of DaT-SPECT to monitor the progression of disease unless these agents are discontinued prior to imaging. Patients with clinically diagnosed PD or DLB, who present with a normal DaT-SPECT scan, are referred to in the literature as having "scans without evidence of dopaminergic deficit." While many of these patients are ultimately diagnosed with non-PD syndromes, a portion of patients with normal DaT-SPECT imaging are confirmed to have PD or DLB by the reference standard. In studies where clinical diagnosis is used as an end point, scans without evidence of dopaminergic deficit are present in 3% to 20% of PD patients. In a study of patients clinically diagnosed with DLB, van der Zande et al (2016) found that 10% of these patients had normal scans. Further research may shed light on these cases.

**FDA or Other Governmental Regulatory Approval**

**U.S. Food and Drug Administration (FDA)**

In 2011, DaTscan™ (GE Healthcare) was approved by the U.S. Food Drug Administration through a new drug application and is “indicated for striatal dopamine transporter visualization using single photon emission computed tomography brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes. In these patients, DaTscan may be used to help differentiate ET [essential tremor] from tremor due to parkinsonian syndromes (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.”

U.S. Food Drug Administration product code: KPS.
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Centers for Medicare and Medicaid Services (CMS)
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.

Rationale/Source
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 Parkinson disease (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 PICOTS 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 end point for the diagnosis of 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 (i.e., tremor, slowness of movements, rigidity, instability), nonmotor symptoms (e.g., mood, fatigue, daytime sleepiness), and quality of life (e.g., limitations in daily activities due to symptoms). Outcomes may also include treatment-related morbidity and mortality, particularly in regards to use of dopaminergic medications.

Timing
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.

Setting
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).

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires 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.

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 end point 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). 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 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; 3 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 end point 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 end point revealed a sensitivity of 78% and specificity of 97%. Comparison of the baseline clinical diagnosis with the reference standard end point 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 end point 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 end point 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 end point 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
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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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Prior DaT-SPECT scan</td>
<td>• Different test performed</td>
</tr>
<tr>
<td>Marshall et al (2009)</td>
<td>10 European sites</td>
<td>• Clinically uncertain PD</td>
<td>• Other potential causes of parkinsonism or tremor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Met criteria for both PS and ET</td>
<td>• Major comorbid illness</td>
<td>• Protocol violations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• UPDRS-III score ≤16</td>
<td>• Iodine sensitivity</td>
<td>• Personal reasons</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Safety or medical reasons</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Loss to follow-up</td>
</tr>
<tr>
<td>Kupsch et al (2012, 2013); Hauser et al (2014); Bajaj et al (2014)</td>
<td>19 U.S. and European centers</td>
<td>• Clinically uncertain, monosymptomatic, atypical, or incomplete presentation with possible parkinsonian syndrome</td>
<td>• Differential diagnosis of PD vs PSP or MSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Early-onset parkinsonian syndrome (&lt;5 y of symptoms)</td>
<td>• Diagnosed movement disorder or cause of tremor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Significant cognitive impairment</td>
<td>• Protocol violations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Medications known to interact with DaT-SPECT scan</td>
<td>• Patient request</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Loss to follow-up</td>
</tr>
</tbody>
</table>


Table 2. Clinical Validity Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Scenario (N)</th>
<th>OR</th>
<th>Sensitivity (95% CI), %</th>
<th>Specificity (95% CI), %</th>
<th>PPV (95% CI), %</th>
<th>NPV (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vlaar et al (2008)</td>
<td>PD (127) vs ET (22)</td>
<td>82</td>
<td>80</td>
<td>95</td>
<td>99</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>PD (127) vs VP (16)</td>
<td>61</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>PD (127) vs DIP (5)</td>
<td>36</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>PD (127) vs APS (27)</td>
<td>1</td>
<td>80</td>
<td>24</td>
<td>87</td>
<td>15</td>
</tr>
<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)</td>
<td>96.8 (83.3 to 99.9)</td>
<td>98.2 (90.1 to 100)</td>
<td>66.2 (49.8 to 80.0)</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)</td>
<td>100 (80.5 to 100)</td>
<td>100 (91.2 to 100)</td>
<td>89.5 (66.9 to 98.7)</td>
</tr>
</tbody>
</table>

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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 Gaps

<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>
<tbody>
<tr>
<td>Vlaar et al (2008)</td>
<td>2. No clear criteria for selection 2. Clinical history sufficient for diagnosis in 154/248 patients 2. 61/248 patients had parkinsonism as only differential diagnosis</td>
<td>2. Unclear criteria for assigning patients for DaT-SPECT by tracers for dopamine transporters and/or receptors</td>
<td>2. Clinical diagnosis performed by both residents and movement specialists 2. Physicians not consistently blinded to DaT-SPECT results</td>
<td>1. No health outcomes reported 2. No clinical decisions described 3. No evidence chain explicated 5. No AEs discussed</td>
<td>1. Insufficient follow-up between initial and final clinical diagnoses to improve clinical accuracy 1. Not all patients had a final diagnosis</td>
</tr>
<tr>
<td>Marshall et al (2009)</td>
<td>3. Patients met criteria for both PS and ET; excludes other causes of parkinsonism</td>
<td></td>
<td></td>
<td>1. No health outcomes reported 2. No clinical decisions described 5. No AEs discussed</td>
<td></td>
</tr>
<tr>
<td>Kupsch et al (2012, 2013); Hauser et al (2014); Bajaj et al (2014)</td>
<td>3. Patients had early uncertain PS; excluded late uncertain PS</td>
<td>2. Clinical diagnosis performed by generalists and movement specialists 2. Physicians not blinded to DaT-SPECT results</td>
<td></td>
<td>1. Insufficient follow-up between initial and final clinical diagnoses to improve clinical accuracy 1. Not all patients had a final diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. AE: adverse event; DaT-SPECT: dopamine transporter imaging with single-photon emission computed tomography; DIP: drug-induced parkinsonism; ET: essential tremor; FU: follow-up; PD: Parkinson disease; PS: parkinsonian syndromes including Parkinson disease, multiple system atrophy, and progressive supranuclear palsy; VP: vascular parkinsonism.

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Table 4. Clinical Validity Study Design and Conduct Gaps

<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)</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. Some p values not reported</td>
<td></td>
</tr>
<tr>
<td>Marshall et al (2009)</td>
<td>1. Selection not described</td>
<td>2. 100 (50%) of 199 patients excluded after enrollment</td>
<td>1. Confidence intervals and p values not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps 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.

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Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Clinically Valid
A meta-analysis of postmortem histopathology studies established expert clinical diagnosis as a reference standard with high sensitivity and low-to-moderate specificity. Studies using this reference standard are limited by gaps 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 physical diagnosis alone. In addition, other DaT-SPECT tracers (e.g., 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-ioflupane; DaTscan) provide supportive evidence for the clinical validity of DaT-SPECT.

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 United States. 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. 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 3 months after a scan revealed no significant difference in the quality of life. Again, health outcomes in the same population at 1 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.

**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 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. 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 10 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). 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. 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 3-month and 1-year follow-up period. Several case series studies have documented 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, Parkinson disease; 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 1 year, clinical input provided additional context that 1-year follow-up may be too short to identify significant changes in quality of life in a slowly progressive condition such as PD.

**TESTING FOR CLINICALLY UNCERTAIN DEMENTIA WITH LEWY BODIES**

**Clinical Context and Test Purpose**

The purpose of DaT-SPECT testing of individuals with uncertain dementia with Lewy bodies (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 PICOTS were used to select literature to inform this review.
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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.

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.

Timing
With the criterion standard of DLB (histopathology), diagnostic accuracy can only be confirmed after death. The reference standard of DLB is clinical diagnosis.

Setting
The criterion setting is a dementia specialist practice for patients undergoing evaluation for DLB and other dementia.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires 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.

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 3 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 limited duration of long-term clinical follow-up to confirm 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 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 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.

**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...
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not considered meaningful health outcomes for this evidence review. 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. 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. 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 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 (e.g., 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 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.

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

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

References

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04/07/2016 Medical Policy Committee review
04/20/2016 Medical Policy Implementation Committee approval. New policy.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017 Medical Policy Committee review
04/19/2017 Medical Policy Implementation Committee approval. No change to coverage.
04/05/2018 Medical Policy Committee review
04/18/2018 Medical Policy Implementation Committee approval. No change to coverage.
01/10/2019 Medical Policy Committee review
01/23/2019 Medical Policy Implementation Committee approval. Policy statement changed to eligible for coverage for clinically uncertain Parkinson disease and clinically uncertain dementia with Lewy bodies.

Next Scheduled Review Date: 01/20 20

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