Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography

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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.

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 dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) to be **investigational*** for all indications, including but not limited to the following:

- Aiding in the diagnosis of patients with clinically uncertain parkinsonian syndromes; OR
- Distinguishing between parkinsonian syndromes (PS) and essential tremor (ET); OR
- Distinguishing between dementia with Lewy bodies (DLB) and Alzheimer disease (AD); OR
- Monitoring of disease progression.

Background/Overview

DOPAMINE TRANSPORTER IMAGING WITH SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY
DaT-SPECT is based on the selective affinity of dopamine transporter ligands for dopamine synthesizing neurons, which allows visualization of deficits in the nigrostriatal dopaminergic pathway.

Dopamine transporter ligands include iodine 123 2β-carbomethoxy-3β-(4-iodophenyl) tropane (^{123}I-β-CIT), which is a cocaine analogue with affinity for both dopamine transporter and serotonin transporters. Intravenous ^{123}I-β-CIT requires a delay between injection and scan of about 24 hours. Iodine 123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (^{123}I-FP-CIT) is a fluoropropyl derivate of β-CIT that is selective for brain striatal dopamine transporter, but can also bind to the serotonin transporter. Intravenous ^{123}I-FP-CIT can be injected 3 to 6 hours before the scan (DaTscan). Other ligands with affinity for dopamine transporter include technetium 99m (2β((N,N′-bis(2-mercaptoethyl) ethylene diamino)methyl) and 3β-(4-chlorophenyl) tropane (^{99m}Tc-TRODAT-1).

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

Visualization of striatal dopamine transporter binding, through DaT-SPECT, permits assessment of presynaptic dopaminergic deficit. It is proposed that an abnormal DaT-SPECT scan supports the diagnosis of PD, DLB, or other neurodegenerative parkinsonian syndrome, while a normal DaT-SPECT scan in a

symptomatic patient supports the diagnosis of a disease not affecting the nigrostriatal dopaminergic pathway. There are, however, a significant percentage of patients with clinically diagnosed PD who do not show reduced DaT-SPECT binding. Scans without evidence of dopaminergic deficit are referred to as SWEDD. Additional research may shed light on these cases.

Analysis of DaT-SPECT images can be visual, semiquantitative, or quantitative. Because patients typically do not become symptomatic before a substantial number of striatal synapses have degenerated, visual interpretation of the scan is thought to be sufficient for clinical evaluation. A variety of methods are being tested to improve the validity and reliability of ratings, including commercially available software to define the region of interest for analysis and the development of an atlas for visual interpretation.

DIAGNOSIS OF PARKINSON DISEASE

Parkinsonian syndromes are a group of diseases that share similar cardinal signs, characterized by bradykinesia, rigidity, resting tremor, and gait disturbance. PD is the most common cause of parkinsonism. Despite the well-known symptoms of PD, diagnosis is challenging even for experienced clinicians, particularly in early stages of the disease. In addition, other etiologies such as essential tremor, corticobasal degeneration, multisystem atrophy, progressive supranuclear palsy, vascular parkinsonism, and drug-induced parkinsonism can lead to a similar set of symptoms.

While the criterion standard is postmortem histopathology, clinical diagnosis may be used as an interim reference standard. Accuracy of the diagnosis is influenced by the duration of the symptoms, in addition to the clinician's experience. Even in specialized movement disorders centers, up to 25% of patients may be misclassified, and some patients (eg, those with essential tremor who have been diagnosed with PD) may be erroneously treated. Such misclassifications have led to the call for additional diagnostic tests and biomarkers to improve the accuracy of clinical diagnosis of PD and other parkinsonian syndromes. One recent approach is to evaluate the integrity of dopaminergic pathways in the brain using DaT-SPECT imaging.

DIAGNOSIS OF DLB

DLB is a type of dementia characterized by parkinsonism, visual hallucinations, cognitive fluctuation, sleep disorders, and severe neuroleptic sensitivity. DLB is the second most common form of degenerative dementia; AD, which can have similar symptoms at onset, is the most common. Diagnosis can be challenging, particularly when patients have multiple comorbidities including cerebrovascular disease and/or AD.

As with PD, DLB is characterized by the degeneration of nigrostriatal neurons; as such, DaT-SPECT is also proposed to differentiate DLB from AD. 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 AD.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In 2011, DaTscan™‡ (GE Healthcare, Chicago, IL) was approved by the U.S. FDA 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. FDA product code: KPS.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes).

The criterion standard for the diagnosis of parkinsonian syndromes and dementia is postmortem neuropathologic examination. In the absence of comparisons with the criterion standard, long-term clinical follow-up may be used as a reference standard to evaluate the ability of DaT-SPECT to discriminate degenerative parkinsonian syndromes from normality or from nondegenerative disorders that present with similar symptoms, and to discriminate DLB from Alzheimer disease.

TESTING FOR CLINICALLY UNCERTAIN PARKINSON DISEASE

Clinical Context and Test Purpose
The purpose of DaT-SPECT testing of individuals with clinically uncertain PD is to include or exclude the diagnosis of PD, 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 health outcomes?

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 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 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 are 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).

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 as well as 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, as well as by 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 thus a tertiary clinic of neurologists specializing in movement disorders (including PD).

Technical Reliability
The technical accuracy of a test is its ability to detect disease that is present or exclude disease that is absent.

DaT-SPECT scans allow visualization of radioligands which bind the presynaptic dopamine transporter (DaT) protein. Anatomic variation in the brain, including vascular lesions, may interfere with 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 progression of disease. 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

imaging for visual analysis to be adequate for interpretation. Several research centers are developing quantitative and semiquantitative classification methods for the evaluation of DaT-SPECT images.

Visual interpretation of DaT-SPECT was assessed in a 2012 study by Papathanasiou et al, which evaluated interobserver variability in classifying normal vs abnormal DaT-SPECT scans. Eighty-nine DaT-SPECT scans were blindly re-reviewed by 3 independent observers with different levels of experience (consultant, resident doctor, radiographer). There was good interobserver agreement for 85 of 89 studies in classifying scans as "normal" or "abnormal" (κ range, 0.89-0.93) and moderate agreement in assignment of uptake scores (κ range, 0.71-0.80 for putamina; 0.50-0.79 for caudate nuclei). In 2014, Seibyl et al reported on intra- and interrater agreement for DaT-SPECT images from 5 multicenter studies (total N=818 patients). In both trials, between-reader agreement was high (κ>0.8) for classifying scans as "normal" or "abnormal". Within-reader agreement was assessed in the Seibyl study, which showed complete (100%) agreement when image evaluation was blinded.

The ability of DaT-SPECT imaging to distinguish between disease states has been described in defined populations. A 2000 multicenter study by Benamer et al included 158 patients with an established clinical diagnosis of parkinsonism (including PD, multiple system atrophy, and progressive supranuclear palsy), 27 cases of definite ET, and 35 healthy volunteers. Striatal uptake of the DaT ligand was graded visually as normal or abnormal by an institutional reader blinded to the clinical data and a blinded consensus panel of 5 readers. The institutional reader scored 154 of 158 cases of parkinsonism as abnormal, all 27 cases of ET as normal, and 34 of 35 healthy volunteers as normal, resulting in sensitivity for parkinsonism of 97% and specificity for ET of 100%. For the consensus blinded read, sensitivity for parkinsonism and specificity for ET were 95% and 93%, respectively.

More recently, Mo et al (2015) prospectively studied the diagnostic accuracy of visual assessment of DaT-SPECT in individuals with early-stage PD. The study included 171 patients with a definitive diagnosis of early-stage PD and 37 age-matched healthy controls. DaT-SPECT scan interpretation was appropriately blinded to clinical input; clinicians assessing diagnosis at the reference standard end point of the study followed clinical guidelines (UK Parkinson Disease Society Brain Bank) for diagnosis but were not, notably, blinded to results from DaT-SPECT scans. There was a discrepancy in DaT-SPECT scan interpretation in 10 (9.3%) cases; these cases were reevaluated for a consensus. Visual interpretation of DaT-SPECT scans had a sensitivity of 94% and a specificity of 92% for the diagnosis of PD. Significantly, 10 of the 171 patients with a clinical diagnosis of Parkinson disease had normal DaT-SPECT scans. At the time of reporting, it was not known whether these cases were true false-negatives or patients with an incorrect reference standard end point (clinical diagnosis of PD).

Patients with clinically diagnosed PD, who present with a normal DaT-SPECT scan, are referred to in the literature as "scans without evidence of dopaminergic deficit" (SWEDD). 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 by the reference standard. In studies where clinical diagnosis is used as an end point, SWEDD is present in 3% to 20% of PD patients. In 2016, Nicastro et al reviewed 410 patients with

parkinsonian symptoms to identify 10 (2.4%) patients with SWEDD; 8 of the 10 continued to be diagnosed with PD. Visual re-review of initial DaT-SPECT scans showed abnormalities in nine of the patients; repeat DaT-SPECT scans of 7 patients with SWEDD showed abnormalities in the second screen. While this would suggest that SWEDD is due to errors in interpreting the DaT-SPECT scan, physicians performing re-review of DaT-SPECT scans were not blinded in this study. A prospective study by Ueda et al in 2017 reviewed 145 patients with parkinsonian symptoms to identify 18 (12.4%) patients with SWEDD, 11 of whom remained with a diagnosis of PD after 2 years of clinical follow-up. This supports the hypothesis that a portion of patients with SWEDD are true false-negatives for PD. Weaknesses of this study included lack of physicians blinding to results of DAT-SPECT imaging.

Section Summary: Technical Reliability
Preclinical studies have indicated the specificity of ligand binding for the striatal DaT. There is limited evidence on the effects of medications on DaT expression. Studies have reported a high level of interobserver agreement on visual interpretation of images for PD, suggesting that the reliability of visual interpretation for this disorder is high. While DaT-SPECT has high sensitivity and specificity in patients who present with classical signs of PD, there is a poorly understood population of patients with clinically diagnosed PD in whom DaT-SPECT scans are normal.

Clinical Validity
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 imaging 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. A meta-analysis of physician diagnosis of PD, relative to histopathology, was published in 2016 by Rizzo et al. 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). 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 less than 3 years, and 53% in another study examining disease duration of less than 5 years.

In 2009, Marshall et al reported on a prospective, investigator-initiated industry-funded, 3-year European multicenter study in 99 diagnostically uncertain cases of PD or 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 imaging at baseline, 18 months, and 36 months was 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 parkinsonism 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 in 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 SWEDD 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 Bajaj et al (2014), Kupsch et al (2012, 2013), and Hauser 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 design and analysis for these studies are detailed in Tables 1, 3, and 4. Three of 5 studies in a 2014 meta-analysis by Brigo et al did not use clinicians blinded to DaT-SPECT scans. One of 4 studies in the 2014 meta-analysis by O'Brien et al 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

Author (Year)	Setting	Selection Criteria	Exclusion Criteria	Drop-Outs
Vlaar et al (2008)	Neurology outpatient clinic (Netherlands)	Patient referral by neurologist	• Clear unequivocal diagnosis of PD prior to ordering DaT-SPECT scan • Prior DaT-SPECT scan	• Diagnosis is unclear • Different test performed
Marshall et al (2009)	10 European sites	• Clinically uncertain PD • Met criteria for both PD (UK Brain Bank) and ET (Findley & Koller) • UPDRS-III score ≤16	• Other potential causes of parkinsonism/tremor • Major comorbid illness • Iodine sensitivity	• Protocol violations • Personal reasons • Safety or medical reasons • Lost to follow-up
Kupsch et al (2012, 2013), Hauser et al (2014), Bajaj et al (2014)	19 U.S. and European centers	• Clinically uncertain, monosymptomatic, atypical, or incomplete presentation with possible parkinsonian syndrome • Early-onset parkinsonian syndrome (<5 y of symptoms)	• 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	• Protocol violations • Patient request • Pretreatment event • Lost to follow-up

DaT-SPECT: dopamine transporter imaging with single-photon emission computed tomography; ET: essential tremor; MSA: multiple system atrophy; PD: Parkinson disease; PSP: progressive supranuclear palsy; UPDRS-III: Unified Parkinson's Disease Rating Scale – Motor.

Table 2. Clinical Validity Study Results

Author (Year)	Scenario (N)	OR	Sensitivity, % (95% CI) [p value]	Specificity, % (95% CI) [p value]	PPV (95% CI), %	NPV (95% CI), %
Vlaar et al (2008)	PD (112) vs ET (21)	82	80	95	99	48
	PD (112) vs VP (14)	61	80	100	100	39
	PD (112) vs DIP (4)	36	80	100	100	15
	PD (112) vs APS (17)	1	80	24	87	15
Marshall et al (2009)	PD (71) vs non-PD[b] (28)	NR	78.0 (66.0 to 87.5) [< 0.001]	96.8 (83.3 to 99.9) [0.002]	98.2 (90.1 to 100) [NR]	66.2 (49.8 to 80.0) [NR]
Kupsch et al (2012, 2013) Hauser et al (2014), Bajaj et al (2014)	PS (49) vs non-PS (43)	NR	95.8 (85.8 to 99.5) [0.134]	93.2 (81.3 to 98.6) [<0.001]	93.9 (83.1 to 98.7) [<0.001]	95.4 (84.2 to 99.4) [0.010]

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; VP: vascular parkinsonism; PS: parkinsonian syndromes including Parkinson disease, multiple system atrophy, and progressive supranuclear palsy.
[a] Only data on the 123I-Ioflupane DaT are reported here; results from the 123I- iodobenzamide tracer were disregarded.
[b] While final diagnosis was not explicated, patients entering the study met criteria for diagnosis of PD and ET.

Table 3. Clinical Validity Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Vlaar et al (2008)	2. No clear criteria for selection 2. Clinical history sufficient for unequivocal diagnosis in 154/248 patients 2. 61/248 patients had PD listed as only differential diagnosis	2. Unclear criteria for assigning patients for SPECT by tracers for dopamine transporters (^{123}I ioflupane) and/or receptors (^{123}I-iodobenzamide)	2. Clinical diagnosis was 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 adverse events discussed	1. Insufficient follow-up between initial and final clinical diagnosis to improve clinical accuracy 1. Insufficient study length to resolve diagnosis in 27/248 patients
Marshall et al (2009)	5. Patients meet criteria for both PD and ET; excludes DIP, VP			1. No health outcomes reported 2. No clinical decisions described 5. No adverse events discussed	
Kupsch et al (2012, 2013),	5. Patients had early uncertain		2. Clinical diagnosis was		1. Insufficient follow-up

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Hauser et al (2014), Bajaj et al (2014)	PS; excluded late uncertain PS		performed by generalists and movement specialists 2. Physicians not blinded to DaT-SPECT results		between initial and final clinical diagnosis to improve clinical accuracy 1. No final clinical diagnosis in 20/112 patients who had DaT-SPECT

DaT-SPECT: dopamine transporter imaging with single-photon emission computed tomography; DIP: drug-induced parkinsonism; ET: essential tremor; PD: Parkinson disease; VP: vascular parkinsonism; 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; [5] Study population is subpopulation of intended use.
[b] Intervention Key: [1] Classification thresholds not defined; [2] Version used unclear.
[c] 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.
[d] 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).
[e] Follow-Up Key: [1] Follow-up duration not sufficient with respect to natural history of disease (TP, TN, FP, FN cannot be determined).

Table 4. Clinical Validity Study Design and Conduct Gaps

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Vlaar et al (2008)		1. Final clinical diagnosis not consistently blinded to scan results	3. Unclear if quantitative, visual, or combined analysis used to interpret scans		1. Unclear what percentage of patients undergoing 123I-Iofluopane scan were excluded after enrollment 3. Variable follow-up pathways; did not always include direct patient exam or interaction	1. p values and confidence intervals not reported
Marshall et al (2009)	1. Selection not described				2. 100/199 (50%) of patients were excluded after enrollment	1. Some p values not reported
Kupsch et al (2012, 2013), Hauser et al (2014), Bajaj et al (2014)	2. Selection not described	1. DaT-SPECT analysis not consistently blinded 1. Clinical end point not			2. 43/135 (32%) of patients assigned to receive DaT-SPECT were excluded after enrollment	

		blinded (per study design)

DAT-SPECT: dopamine transporter imaging with single-photon emission computed tomography.
[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.
[d] Selective Reporting Key: [1] Not registered; [2] Evidence of selective reporting; [3] Evidence of selective publication.
[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 to other tests not reported.

Section Summary: Clinical Validity
The literature on clinical validity does not include any studies using the criterion standard of postmortem histopathology. A meta-analysis of postmortem histopathology studies establishes expert clinical diagnosis as a reference standard with high sensitivity and low-to-moderate specificity. A large industry-sponsored study using this reference standard to assess the diagnostic accuracy of DaT-SPECT indicated that DaT-SPECT has moderate sensitivity and high specificity. The high PPV indicates that, in a population of patients with a high pretest likelihood of PD, a positive test may be useful in confirming PD. However, the low NPV indicates that a negative test is less useful in ruling out the disorder.

Clinical Utility
The most rigorous evaluation of the impact of a diagnostic test on health outcomes is a randomized controlled trial (RCT) that evaluates 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 reported in 2012 and 2013 on an industry-sponsored, open-label, multicenter randomized trial from 19 university hospital centers in Europe and the United States. This report 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 is reviewed in Tables 1 through 4. Patients were randomized to DaT-SPECT (n=109) or no imaging (n=123), with DaT-SPECT imaging 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 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 difference in the quality of life or health resource utilization between those who received a DaT-SPECT scan, and those who did not.

A chain of evidence demonstrating that DaT-SPECT imaging 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.

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, who were 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 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 imaging with the reference standard (clinical diagnosis over sufficient time), which would validate treatment decisions, was provided. Specific health outcomes resulting from 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. Weaknesses of this study 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 imaging. 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 imaging results.

Several studies were excluded from our review because they lacked appropriate health outcome metrics, as described above. Two of these studies 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: Clinical Utility

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 with DaT-SPECT had no improvement in health outcomes, when compared to those who were not evaluated with 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 imaging to improved patient outcome cannot be constructed.

TESTING FOR CLINICALLY UNCERTAIN DEMENTIA WITH LEWY BODIES

Clinical Context and Test Purpose

The purpose of use of DaT-SPECT testing of individuals with uncertain DLB is to establish the clinical diagnosis of DLB 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 health outcomes?

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

Patients

The populations of interest include individuals with uncertainty in diagnosis of DLB after assessment by a specialist in dementia disorders. It would also include patients with a continuing diagnostic dilemma of DLB vs AD.

Interventions

The relevant intervention of interest is DaT-SPECT, used as a diagnostic adjunct to 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.

Technical Reliability
The technical reliability of the test is its ability to detect disease that is present or exclude disease that is absent.

In DLB, loss of dopaminergic neurons is associated with the accumulation of Lewy bodies within dopaminergic neurons; patients with DLB would thus be expected to have abnormal DaT-SPECT imaging. Visual interpretation of abnormal DaT-SPECT scans for patients with dementia was assessed in a 2007 study by McKeith et al. DaT-SPECT scans of 326 patients with probable, possible, or non-DLB were reviewed by 3 nuclear medicine physicians with expertise in DaT-SPECT interpretation, who were blinded to clinical diagnosis. Interreader agreement was moderately high (κ>0.87) for rating scans as normal or abnormal.

A 2015 meta-analysis by Brigo et al evaluated the diagnostic accuracy of DaT-SPECT in distinguishing between DLB and other dementias. Eight studies were included, of which three used histopathology as the reference standard. Studies that used clinical diagnosis as the reference standard showed diagnostic accuracy above 80% when using visual or semiquantitative analysis (see Table 5). The 2 studies using a histopathologic reference standard and visual analysis showed similar sensitivity (87%) and slightly higher specificity (92%) compared with studies that used clinical diagnosis as the reference standard. The single study that used semiquantitative analysis with histopathology as a reference standard correctly identified the 15 patients with DLB (100% sensitivity) and had 90% specificity in the identification of the 8 patients with non-DLB dementia. The small population studied (N=23) is a weakness of this study.

Table 5. Accuracy of DaT-SPECT in the Differential Diagnosis of DLB vs Non-DLB Dementia

Analysis	Reference Standard	Sensitivity, %	Specificity, %	No. of Studies
Visual	Clinical diagnosis	87	84	6
Semiquantitative	Clinical diagnosis	79	86	4
Visual	Histopathology	87	92	2
Semiquantitative	Histopathology	100	90	1

DaT-SPECT: dopamine transporter imaging with single-photon emission computed tomography; DLB: dementia with Lewy bodies.

A 2017 study by Thomas et al prospectively evaluated the diagnostic accuracy of clinical diagnosis and DaT-SPECT with an endpoint of postmortem histopathology. Patients (N=55) were recruited from memory and dementia services and gave consent for neuropathologic analysis of brain tissue. Patients who had a diagnosis of likely DLB or Alzheimer disease, and who had received a DaT-SPECT scan, were selected from this population. No healthy controls were present. Clinical diagnosis at the time of DaT-SPECT imaging was recorded. Clinicians were blinded to DaT-SPECT interpretation, and vice versa; in addition, pathologic diagnosis was blinded to both clinical diagnosis and DaT-SPECT scans. Of note, several

patients had a diagnosis of mixed DLB and Alzheimer disease by histopathology. Clinical diagnosis had a sensitivity of 87% and a specificity of 72%, compared with histopathology. DaT-SPECT imaging had a sensitivity of 80% and a specificity of 92%, compared with histopathology.

Several studies have followed patients with inconsistent results from DaT-SPECT and clinical diagnosis. In 2013, Siepel et al reported on a longitudinal study of patients who had inconsistent clinical criteria for DLB and DaT-SPECT results at baseline. Fifty patients were evaluated with clinical criteria and DaT-SPECT results and followed for 2 to 5 years. Twenty-eight patients met clinical criteria for DLB or non-DLB; the remaining patients were clinically inconclusive and not included in the analysis. For 18 patients, the DaT-SPECT scan and clinical criteria were concordant. Blinded analysis showed 7 patients who had an abnormal scan but did not initially meet the clinical criteria for DLB developed typical clinical features over follow-up. Three patients who met clinical criteria for DLB but had a normal DaT-SPECT at baseline continued to meet clinical criteria for DLB over follow-up, indicating a false-negative scan (SWEDD) in 6% of patients. Van der Zande et al (2016) reported on 7 (10.4%) of 67 patients who were clinically diagnosed with DLB but had normal scans. In 5 of the 7 patients, repeat DaT-SPECT scans (average 1.5 years later) were abnormal. There were no differences in baseline clinical characteristics, but patients with initially normal scans were less severely affected after 1 year. These studies evaluated small numbers of subjects and lacked autopsy findings to confirm the diagnosis.

More recently, several research centers have focused on developing quantitative and semiquantitative classification methods for the evaluation of DaT-SPECT images.

Clinical Validity
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 imaging in patients with clinically uncertain DLB.

The largest study to evaluate DaT-SPECT for DLB is a 2007 prospective, investigator-initiated, industry-sponsored, multicenter study by McKeith et al (mentioned above). 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 imaging 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 study did not use long-term clinical follow-up as the standard.

Clinical Utility
The most rigorous evaluation of the impact of a diagnostic test on health outcomes is an RCT that evaluates health outcomes in patients with clinically uncertain DLB who received the new diagnostic test compared with patients who received the standard of care. Health outcomes are defined here 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. 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 imaging.

Several studies were excluded from our review because they lacked appropriate health outcome metrics. An RCT by Walker et al (2015) reviewed diagnostic change and diagnostic confidence alone, which is not considered as meaningful health outcomes in our 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.

Section Summary: Clinical Utility
No studies on the impact of DaT-SPECT imaging on clinical outcomes have been published. Therefore, a chain of evidence linking DaT-SPECT imaging to improved patient outcome cannot be constructed.

SUMMARY OF EVIDENCE
For individuals who have clinically uncertain Parkinson disease who receive DaT-SPECT, the evidence includes randomized controlled trials, cohort studies, and case series studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. Studies of technical validity have shown good interobserver reliability in interpreting images. In populations with clinically apparent Parkinson disease, studies of diagnostic accuracy have reported high sensitivity and specificity for Parkinson disease. Studies of clinical validity in the target population of clinically uncertain Parkinson disease have reported moderate sensitivity and high specificity. These findings are dependent on a reference standard (clinical diagnosis over time), and it is unknown whether DAT-SPECT would show greater sensitivity when assessed by the criterion standard (histopathologic diagnosis). Evidence on clinical utility in the target population includes a randomized controlled trial showing no significant difference in outcomes over time between patients who received a DaT-SPECT scan and those who did not. The evidence is insufficient to determine the effects of this technology on health outcomes.

For individuals who have clinically uncertain dementia with Lewy bodies who receive DaT-SPECT, the evidence includes randomized control trials, cohort studies, and case series studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. Relative to the criterion end point of histopathology, DaT-SPECT has lower sensitivity and higher specificity than expert clinical diagnosis in patients with likely dementia with Lewy bodies. No such studies have been performed in the target population of clinically uncertain dementia with Lewy Bodies. No studies have directly evaluated the

effect of DaT-SPECT imaging on health outcomes in the target population. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

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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
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