6.01.54 Dopamine Transporter Single-Photon Emission Computed Tomography			
Original Policy Date:	June 28, 2013	**Effective Date:**	January 1, 2024
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Policy Statement

I. Dopamine transporter imaging with single-photon emission computed tomography may be considered **medically necessary** when used for individuals with:
   A. Clinically uncertain Parkinson disease
   B. Clinically uncertain dementia with Lewy bodies

II. Use of dopamine transporter imaging with single-photon emission computed tomography is considered **investigational** for all other indications not included above.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

In July 2021, aducanumab (Aduhelm™; Biogen) received FDA accelerated approval and in July, 2023, lecanemab-irmb- (Leqembi; Esai) received FDA approval as amyloid beta-targeted antibodies for the treatment of mild cognitive impairment or mild dementia due to Alzheimer disease. The safety and efficacy of aducanumab or lecanemab in individuals with dementia with Lewy bodies has not been established as participants with any medical or neurological condition other than Alzheimer disease that might be a contributing cause to the subject's cognitive impairment were excluded from trials. The use of dopamine transporter imaging with single-photon emission computed tomography for the diagnosis, management, or surveillance of Alzheimer disease is considered out of scope for this policy.

Description

Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), using radiopharmaceutical ioflupane injection, is a neuroimaging modality being evaluated to improve the differential diagnosis of parkinsonian syndromes from nonparkinsonian tremor, as well as dementia with Lewy bodies from Alzheimer disease.

Related Policies

- Deep Brain Stimulation
- Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography
- Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these

instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 2011, DaTscan™ (GE Healthcare) was approved by the U.S. Food Drug Administration (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."[13,]

In July 2021, aducanumab (Aduhelm™; Biogen), an amyloid beta-targeted antibody, was approved for the treatment of mild cognitive impairment or mild dementia due to Alzheimer disease. The safety and efficacy of aducanumab in patients with dementia with Lewy bodies has not been established as patients with any medical or neurological condition other than Alzheimer disease that might be a contributing cause to the subject's cognitive impairment were excluded from trials. The use of DaT-SPECT for the diagnosis, management, or surveillance of Alzheimer disease is considered out of scope for this policy.

FDA product code: KPS.

Rationale

Background

Parkinsonian Syndromes

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.

Despite the well-known symptoms of PD, diagnosis is challenging even for experienced clinicians, particularly in the early stages of the disease. In addition, other etiologies such as essential tremor, corticobasal degeneration, multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism, and drug-induced parkinsonism can lead to a similar set of symptoms. One recent approach to improve the accuracy of clinical diagnosis of PD and other parkinsonian syndromes 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 is a type of dementia characterized by parkinsonism, visual hallucinations, cognitive fluctuation, sleep disorders, and severe neuroleptic sensitivity. Dementia with Lewy bodies is the second most common form of degenerative dementia; Alzheimer disease, which can have similar symptoms at onset, is the most common.

Diagnosis can be challenging, particularly when patients have multiple comorbidities including cerebrovascular disease and/or Alzheimer disease.[1,] As with PD, dementia with Lewy bodies is characterized by the degeneration of nigrostriatal neurons; as such, DaT-SPECT is also proposed to differentiate dementia with Lewy bodies from Alzheimer disease.

DaT-SPECT

DaT-SPECT is based on the selective affinity of dopamine transporter (DaT) ligands for dopamine-synthesizing neurons, which allows visualization of deficits in the nigrostriatal dopaminergic pathway.

DaT ligands include iodine 123I-2β-carbomethoxy-3β-(4-iodophenyl) tropane (^{123}I-β-CIT), which is a cocaine analogue with an affinity for both dopamine 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 DaT 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 SPECT 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).[2,3,]

Binding of ligands with an affinity for DaT ligands in the striatum is, in general, reduced in PD, genetic parkinsonism, dementia with Lewy bodies, corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy. In contrast, striatal DaT ligand binding is expected to be within the normal range of Alzheimer disease, essential tremor, dystonic tremor, orthostatic tremor, drug-induced parkinsonism, and psychogenic parkinsonism.[2,]

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, dementia with Lewy bodies, or other neurodegenerative parkinsonian syndromes, while a normal DaT-SPECT scan in a symptomatic patient supports the diagnosis of a disease not affecting the nigrostriatal dopaminergic pathway.

Analysis of DaT-SPECT images can be visual, semiquantitative, or quantitative. In patients with PD, physical symptoms start after 30% to 50% of dopaminergic neurons have degenerated.[4,5,] 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.[6,7,8,9,]

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.[10,] 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 dementia with Lewy bodies, 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 dementia with Lewy bodies by the reference standard. In studies where clinical diagnosis is used as an endpoint, scans without evidence of dopaminergic deficit are present in 3% to 20% of PD patients.[11,] In a study of patients clinically diagnosed with dementia with Lewy bodies, van der Zande et al (2016) found that 10% of these patients had normal scans.[12,] Further research may shed light on these cases.

Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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) is to differentiate essential tremor (ET) from tremor due to parkinsonian syndromes in order to guide appropriate management decisions. Specifically, in patients for whom the diagnosis of ET versus Parkinson Disease (PD) is unclear after clinical evaluation who later develop signs of suggestive of PD, ruling out parkinsonian syndromes with DaT-SPECT may minimize unnecessary dopaminergic treatment.

Diagnosis of Essential Tremor

The diagnostic criteria for ET from the International Parkinson and Movement Disorder Society (IPMDS) task force requires isolated tremor consisting of bilateral upper limb action (kinetic and postural) tremor, without other motor abnormalities that is at least 3 years in duration and with or without tremor in other locations along with the absence of other neurologic signs.[14,]

Diagnosis of Parkinson Disease

The clinical diagnosis criteria for PD from the Movement Disorder Society (MDS) consists of an essential criterion, supportive criteria, exclusion criteria and red flags.[15,] The essential criterion is parkinsonism, defined as bradykinesia, in combination with either rest tremor or rigidity. The supportive criteria are: clear and dramatic beneficial response to dopaminergic therapy; levodopa-induced dyskinesia; rest tremor of a limb; and either olfactory loss or cardiac sympathetic denervation. There are 9 absolute exclusion criteria, any one of which rule out PD, and 10 red flags criteria. A diagnosis of clinically established PD requires the essential criterion, absence of any absolute exclusion criteria, at least 2 supportive criteria, and no red flags. A diagnosis of clinically probable PD requires the essential criterion plus the absence of absolute exclusion criteria, and if there are red flags, these must be counterbalanced by supportive criteria.

The following PICO was used to select literature to inform this review.

Populations

The populations of interest include individuals for whom the diagnosis of ET versus PD is unclear after clinical evaluation, in particular, patients suspected of having ET who develop signs suggestive of PD.

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 diagnostic criteria for diagnosis of ET are clinical criteria.

The criterion standard for the diagnosis of PD is postmortem neuropathologic examination. In the absence of a criterion standard, clinical evaluation by general neurologists or expert clinicians and observation over time may be used as an interim reference standard endpoint for the diagnosis of PD. The accuracy of PD diagnosis is affected by clinician expertise and the duration of symptoms. While patients may be initially referred to a general neurologist, there is a statistically significant difference in diagnostic specificity between a generalist and a movement disorder specialist.[16,] Even

in specialized movement disorders centers, up to 25% of patients may be misclassified, and some patients (e.g., those with ET who have been diagnosed with PD) may be erroneously treated.[17,]

A meta-analysis of physician diagnosis of PD, relative to histopathology, was published in Rizzo et al (2016).[16,] Clinical diagnosis of PD by expert clinicians had a sensitivity of 81.3% and a specificity of 83%, as assessed by criterion standards (histopathology). Notably, clinical diagnosis by general neurologists had a sensitivity of 89.7% and a specificity of 49.2%, as assessed by criterion standards (histopathology) or reference standards (diagnosis by experts). The accuracy of clinical diagnosis was also relative to the duration of symptoms. The positive predictive value was listed as 26% in a study examining the disease duration of fewer than 3 years, and 53% for disease duration of fewer than 5 years.

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.[18,] 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 the use of dopaminergic medications.

With the criterion standard of diagnosis 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 to 13.8 years) is useful for improving clinical diagnostic accuracy.[16,]

The diagnostic criteria for ET require tremors of at least 3 years in duration.

Study Selection Criteria

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

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard; preference is given to studies with a reference standard of postmortem neuropathologic examination or clinical diagnosis with at least 3 years of follow-up
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.
- Diagnostic studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic [ROC], area under ROC [AUROC], c-statistic, likelihood ratios) may be included but are less informative.

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 through 4).

Studies of clinical validity for DaT-SPECT in diagnosing PD rely on the reference standard endpoint of diagnosis by a clinician, based on physical diagnosis and patient history; preference is given to studies with at least 3 years of follow-up.

Review of Evidence

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 ET.[19,] 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 to 0.97). The baseline clinical diagnosis and reference standard endpoint was video analysis of the patient, at the start of the study and after 36 months, by movement disorder specialists who were blinded to imaging data and patient history. Comparison of the baseline DaT-SPECT scans with the reference standard endpoint revealed a sensitivity of 78% and specificity of 97%. Comparison of the baseline clinical diagnosis with the reference standard endpoint showed a sensitivity of 93% and specificity of 46%. Of the 71 patients with clinical diagnosis of parkinsonian syndrome (including PD, multiple system atrophy, and progressive supranuclear palsy) at the end of this study, 1 patient had a DaT-SPECT scan that changed from normal to abnormal between the baseline and the scan at 36 months, and 1 patient had a DaT-SPECT scan that changed from abnormal to normal at the same time. Both patients were clinically diagnosed with PD. Of note, 15 (21%) patients with a clinical diagnosis of PD had unexpectedly normal DaT-SPECT imaging at baseline, 18 months, and 36 months. It is not known whether these cases of scans without evidence of dopaminergic deficit resulted from a false-negative DaT-SPECT scan or an incorrect reference standard endpoint of clinical diagnosis. Strengths and weaknesses of this study are detailed in Tables 1, 3, and 4.

Vlaar et al (2008) retrospectively reviewed a population of patients with clinically uncertain PD but the reference standard endpoint did not use clinicians blinded to DaT-SPECT scans.[20,] Publications by Kupsch et al (2012, 2013),[21,22,] Hauser et al (2014),[23,] and Bajaj et al (2014),[24,] derive from a common data set on clinically uncertain parkinsonian syndrome (including PD, multiple system atrophy, and progressive supranuclear palsy), which did not use clinicians blinded to DaT-SPECT scans. Further strengths and weaknesses in study designs and analyses for these studies are detailed in Tables 1, 3, and 4. Three of 5 studies in a meta-analysis by Brigo et al (2014) did not use clinicians blinded to DaT-SPECT scans.[25,] One of 4 studies in the meta-analysis by O'Brien et al (2014) did not use clinicians blinded to DaT-SPECT scans.[26,] 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 Characteristics

Study	Sites	Selection Criteria	Exclusion Criteria	Missing Data
Vlaar et al (2008)[20,]	1 European site	Referral by neurologist	• Clear, unequivocal diagnosis prior to ordering DaT-SPECT scan • Prior DaT-SPECT scan	• Final diagnosis unclear • Different test performed
Marshall et al (2009)[19,]	10 European sites	• Clinically uncertain PD	• Other potential causes of	• Protocol violations

Study	Sites	Selection Criteria	Exclusion Criteria	Missing Data
		• Met criteria for both PS and ET • UPDRS-III score ≤16	parkinsonism or tremor • Major comorbid illness • Iodine sensitivity	• Personal reasons • Safety or medical reasons • Loss to follow-up
Kupsch et al (2012, 2013)[21,22]; Hauser et al (2014)[23]; Bajaj et al (2014)[24]	19 U.S. and European centers	• Clinically uncertain, monosymptomatic, atypical, or incomplete presentation with possible PS • Early-onset PS (<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 • Loss to follow-up

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

Table 2. Clinical Validity Study Results

Study	Scenario (N)	OR	Sensitivity (95% CI), %; p	Specificity (95% CI), %; p	PPV (95% CI), %; p	NPV (95% CI), %; p
Vlaar et al (2008)[20,a]	• PD (127) vs ET (22) • PD (127) vs VP (16) • PD (127) vs DIP (5) • PD (127) vs APS (27)	• 82 • 61 • 36 • 1	• 80 • 80 • 80 • 80	• 95 • 100 • 100 • 24	• 99 • 100 • 100 • 87	• 48 • 39 • 15 • 15
Marshall et al (2009)[19]	PS (71) vs non-PS (28)	NR	78.0 (66.0 to 87.5) <.001	96.8 (83.3 to 99.9) .002	98.2 (90.1 to 100) NR	66.2 (49.8 to 80.0) NR
Kupsch et al (2012, 2013)[21,22]; Hauser et al (2014)[23]; Bajaj et al (2014)[24]	PS (42) vs ET (17)	NR	95.2(83.8 to 99.4) 1.00	100(80.5 to 100) .48	100 (91.2 to 100) .14	89.5 (66.9 to 98.7) .3

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 Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Vlaar et al (2008)[20,]	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	2. Unclear criteria for assigning patients for DaT-SPECT by tracers for dopamine transporters and/or receptors	2. Clinical diagnosis performed by both residents and movement specialists 2. Physicians not consistently blinded to DaT-SPECT results	1. No health outcomes reported 2. No clinical decisions described 3. No evidence chain explicated 5. No AEs discussed	1. Insufficient follow-up between initial and final clinical diagnoses to improve clinical accuracy 1. Not all patients had a final diagnosis
Marshall et al (2009)[19,]	3. Patients met criteria for both PS and ET; excludes other causes of parkinsonism			1. No health outcomes reported 2. No clinical decisions described 5. No AEs discussed	
Kupsch et al (2012, 2013)[21,22,]; Hauser et al (2014)[23,]; Bajaj et al (2014)[24,]	3. Patients had early uncertain PS; excluded late uncertain PS		2. Clinical diagnosis performed by generalists and movement specialists 2. Physicians not blinded to DaT-SPECT results		1. Insufficient follow-up between initial and final clinical diagnoses to improve clinical accuracy 1. Not all patients had a final diagnosis

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

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

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

[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 (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 4. Clinical Validity Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Vlaar et al (2008)[20,]		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. Confidence intervals and p values not reported
Marshall et al (2009)[19,]	1.Selection not described				2. 100 (50%) of 199 patients excluded after enrollment	1. Some p values not reported
Kupsch et al (2012, 2013)[22,21,]; Hauser et al (2014)[23,]; Bajaj et al (2014)[24,]	2.Selection not described	1. DaT-SPECT analysis not consistently blinded 1. Clinical endpoint not blinded (per study design)			2. 43 (32%) of 135 patients assigned to receive DaT-SPECT excluded after enrollment	

DAT-SPECT: dopamine transporter imaging with single-photon emission computed tomography.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., 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 with other tests not reported.

Clinically Useful

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

Direct Evidence

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

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

Kupsch et al (2012, 2013) reported on an open-label, multicenter randomized trial from 19 university hospital centers in Europe and the U.S.[22,21,] 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.[21,22,23,24,] 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.[22,] 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.[21,]

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 (negative predictive value [NPV], positive predictive value [PPV]) of the DaT-SPECT test, relative to the reference standard, resulting 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. While a meta-analysis of 13 studies utilizing DaTscan (N=950) by Bega and coworkers (2021) reported a change in management in 54% of patients (95% confidence interval [CI], 47% to 61%; I^2 = 85%; p<.01), corresponding impacts on health outcomes were not reported.[27,]

Case Series

Sadasivan and Friedman (2015) reported on a case series of patients with the clinically uncertain parkinsonian syndrome (N=65), including PD, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration, who were referred for DaT-SPECT over a 17-month period.[28,] 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).[29,] 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.[30,] Patients were classified by diagnostic dilemma, including PD versus ET (n=18), PD versus drug-induced parkinsonism (n=18), or PD versus 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 [31,32,]; while imaging changed diagnosis and management, neither study detailed these outcomes relative to specific diagnostic changes.

Section Summary: Clinically Uncertain Parkinson Disease

A meta-analysis of postmortem histopathology studies established an expert clinical diagnosis as a reference standard with high sensitivity and low-to-moderate specificity. Studies using this reference standard are limited by limitations in study designs, conduct, and relevance. Specific areas of concern include unclear study populations, missing data, insufficient follow-up, and inconsistent blinding. The diagnostic accuracy of DaT-SPECT cannot be determined from these studies.

Evidence 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 a change in diagnosis and management but did not comment on health outcomes. One case series evaluating neurodegenerative parkinsonian syndromes, including PD, indicated that changes based on imaging scans resulted in stable or improved health outcomes, but lacked an appropriate reference standard to evaluate whether changes were made in the direction of more accurate diagnosis and more appropriate management. Therefore, a chain of evidence linking DaT-SPECT to improved patient outcome cannot be constructed.

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 is to establish the clinical diagnosis of dementia with Lewy bodies in order to guide appropriate management decisions.

Diagnosis of Dementia with Lewy Bodies

The Consortium on Dementia with Lewy Bodies has developed consensus criteria for the clinical diagnosis of dementia with Lewy bodies.[33,] Clinical signs and symptoms of dementia with Lewy bodies are organized into a hierarchy, based on diagnostic specificity, of essential, core and supportive features. Biomarkers are categorized as supportive or indicative. The criteria are summarized briefly in Tables 5 and 6 below; see the McKeith (2017) for complete criteria.

Table 5. Hierarchy of Clinical Features and Biomarkers from The Consortium on Dementia with Lewy Bodies

Level of Hierarchy	Feature
Clinical Features	
Essential	• Diagnosis of dementia
Core	• Fluctuating cognition; pronounced variation in attention and alertness
•	• Recurrent visual hallucinations
•	• REM sleep behavior disorder
•	• Parkinsonism: Bradykinesia, rest tremor, or rigidity
Supportive	• Severe sensitivity to antipsychotic agents
•	• Postural instability
•	• Repeated falls
•	• Syncope or transient episodes of unresponsiveness
•	• Severe autonomic dysfunction (e.g., constipation, orthostatic hypotension, urinary incontinence)

Level of Hierarchy	Feature
•	• Hypersomnia
•	• Hyposmia
•	• Hallucinations or delusions
•	• Apathy, anxiety, and depression
Biomarkers	
Indicative	• Reduced dopamine transporter uptake in basal ganglia (SPECT or PET SPECT or PET)
•	• Reduced uptake on metaiodobenzylguanidine myocardial scintigraphy
•	• Polysomnographic confirmation of REM sleep without atonia
Supportive	• Relative preservation of medial temporal lobe structures on CT/ MRI scan
•	• Generalized low uptake on SPECT/PET perfusion/metabolism scan, reduced occipital activity, and the posterior cingulate island sign on FDG-PET imaging
•	• Prominent posterior slow-wave EEG activity with periodic fluctuations in the pre-alpha/theta range

CT: computed tomography; EEG: Electroencephalography; FDG-PET: Fluorodeoxyglucose-Positron Emission Tomography; MRI: magnetic resonance imaging; PET: positron-emission tomography; REM: Rapid Eye Movement; SPECT: Single Photon Emission Computed Tomography;

Table 6. Consensus Criteria for the Clinical Diagnosis from The Consortium on Dementia with Lewy Bodies

Diagnosis	Criteria
Probable dementia with Lewy bodies	2 or more core clinical features of dementia with Lewy bodies are present, with or without indicative biomarkers; OR· Only 1 core clinical feature is present, but with 1 or more indicative biomarkers
Possible dementia with Lewy bodies	Only 1 core clinical feature of dementia with Lewy bodies is present, with no indicative biomarker evidence; OR· 1 or more indicative biomarkers are present, but there are no core clinical features
Dementia with Lewy bodies is less likely	In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture· If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia

Treatment of Dementia with Lewy Bodies

There are no treatments for dementia with Lewy bodies that have been shown to have disease-modifying effects. Treatment of dementia with Lewy bodies is symptomatic. Nonpharmacologic and behavioral therapies may be used. Although the evidence of effectiveness is limited for dementia with Lewy bodies, cholinesterase inhibitors may be used for cognitive and behavioral symptoms, levodopa may be used for parkinsonism symptoms, and other medications may be used for sleep problems and hypotension.

Antipsychotic use is a risk factor for mortality among people with dementia, in general. However, there is potential for severe adverse reactions to antipsychotic (neuroleptic) medications, particularly first-generation antipsychotics, for patients with dementia with Lewy bodies, including exacerbation of parkinsonism, severe confusion, heavy sedation, and even death.

The following PICO was used to select literature to inform this review.

Populations
The populations of interest include individuals with an uncertain diagnosis of dementia with Lewy bodies after assessment by a specialist in dementia disorders. The population would also include patients with an ongoing diagnostic dilemma of dementia with Lewy bodies versus Alzheimer disease (AD).

Based on the diagnostic criteria shown previously in Tables 5 and 6 , the following describes populations that could be evaluated for dementia with Lewy bodies and the potential use of DaT-SPECT for each population (Table 7).

Table 7. Potential Dementia with Lewy Bodies Populations for Consideration

Population	*Potential Diagnostic Use of DaT-SPECT*
1. Patients with dementia having 2 or more *core* clinical features of dementia with Lewy bodies	Patient meets criteria for probable dementia with Lewy bodies without DaT-SPECT
2. Patients with dementia having only 1 *core* clinical feature	DaT-SPECT can aid in distinguishing between possible and probable dementia with Lewy bodies
3. Patients with dementia having no *core* clinical features but 1 or more *suggestive* features	DaT-SPECT can aid in diagnosing possible dementia with Lewy bodies

DAT-SPECT: dopamine transporter imaging with single-photon emission computed tomography.

Population 1 (patients having 2 or more *core* clinical features of dementia with Lewy bodies) meets criteria for probable dementia with Lewy bodies; these patients do not have an uncertain diagnosis and therefore are not part of the population of interest for this review. Population 2 (patients having only 1 *core* clinical feature) meets the criteria for possible or probable dementia with Lewy bodies, both of which are treated symptomatically and therefore distinguishing between possible and probable is unlikely to lead to changes in management decisions and would not be the population of interest for this review. Population 3 (patients having no core clinical features but 1 or more suggestive features) would be the primary population of interest.

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

The U.S. regulatory approval does not include an indication describing how DaT-SPECT should be interpreted in dementia with Lewy bodies.

Comparators
The criterion standard for the diagnosis of dementia with Lewy bodies 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 dementia with Lewy bodies. However, the use of clinical diagnosis as reference standard is a major limitation. The sensitivity of the clinical criteria compared to the postmortem neuropathological is too low for the criteria to be a satisfactory standard.
In addition, DaT-SPECT scans are intended to be used as an adjunct to clinical assessment so studies with clinical diagnosis as the reference standard cannot demonstrate improvement in accuracy above clinical diagnosis and therefore have limited usefulness.

Outcomes
Health outcomes are defined as disease-related morbidity, functional outcomes, and treatment-related mortality and morbidity. Assessment of dementia with Lewy bodies may include tests such as the Lewy Body Composite Risk Score, [34,] which assesses motor symptoms (i.e., rigidity, postural instability) and non-motor symptoms (i.e., daytime sleepiness, hallucinations). Assessment of

dementia with Lewy bodies may also include general tests for dementia including the Clinical Dementia Rating test.

With the criterion standard for diagnosis of dementia with Lewy bodies (histopathology), diagnostic accuracy can only be confirmed after death.

The correct dementia clinical diagnosis may become more evident over time for some types of dementia. As dementia with Lewy bodies progresses, however, the symptoms converge with other types of dementia. Therefore, clinical diagnosis may become less discriminating with time and delayed verification designs using clinical diagnosis at follow-up as the reference standard may not be appropriate.

Study Selection Criteria

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

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard; preference is given to studies with a reference standard of postmortem neuropathologic examination
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort
- Diagnostic studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.

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.

Review of Evidence

Studies with Postmortem Neuropathologic Examination Reference Standard

McCleery et al (2015) reported a Cochrane systematic review of DaT-SPECT for the diagnosis of dementia with Lewy bodies that included neuropathological diagnosis at autopsy as the reference standard.[35,] The review included papers published through 2013. Only 1 study (Walker 2009) was identified and is described in more detail below.

Primary studies evaluating the diagnostic accuracy of DaT-SPECT with postmortem neuropathologic examination as the reference standard are shown in Tables 8 through 11 and briefly described in the following paragraphs. Walker et al (2009) included 22 patients who were diagnosed clinically with dementia with Lewy bodies or AD.[36,] The DaT-SPECT visual ratings were independently performed by 3 raters. The raters classified each scan as 0 (normal uptake), 1 (slightly reduced uptake), or 2 (significantly reduced uptake). Scores of 0 or 1 were defined as a normal scan and a score of 2 was defined as an abnormal scan.

An additional study with postmortem neuropathologic examination as the reference standard has been published since the Cochrane review. Thomas et al (2017) included 55 patients with clinical diagnosis of dementia with Lewy bodies or AD.[37,] The scans were visually rated by 3 to 5 independent raters who were blinded to clinical information. The raters came to a consensus classification of

either abnormal or normal. The sensitivity of clinical diagnosis was 87% (95% CI, 96 to 70) for diagnosing dementia with Lewy bodies.

Table 8. Study Characteristics of Clinical Validity Studies of DaT-SPECT with Postmortem Neuropathologic Exam as the Reference Standard

Study	Study Population	Design	Timing of Reference and DaT-SPECT Tests	Blinding of Assessors
Walker (2009)[36,]	• Secondary care setting in London, United Kingdom • 22 patients with dementia who were diagnosed clinically with dementia with Lewy bodies or AD· • 70% women • Mean age >75 • Moderately severe dementia	Prospective	Mean interval between DaT-SPECT and postmortem exam was 42 months (range, 6 to 106 months)	Yes
Thomas (2017) [37,]	• Newcastle Brain Tissue Resource, United Kingdom • 55 patients with dementia who were clinically diagnosed with dementia with Lewy bodies or AD • Age 60 and older	Prospective	Mean interval between DaT-SPECT and death was 3.3 yr in dementia with Lewy bodies patients and 7.1 yr in AD patients	Yes

AD: Alzheimer disease; DaT-SPECT: dopamine transporter imaging with single-photon emission computed tomography.

Table 9. Study Results of Clinical Validity Studies of DaT-SPECT with Postmortem Neuropathologic Exam as the Reference Standard

Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition	Clinical Validity (95% Confidence Interval)			
					Sensitivity	Specificity	PPV	NPV
Walker (2009)[36,]	Unclear	23	Unclear	41%	100 (66 to 100)	92 (64 to 100)	90 (58 to 98)	100 (70 to 100)
Thomas (2017) [37,]	Unclear	55	Unclear	55%	80 (62 to 92)	92 (74 to 99)	92 (76 to 98)	79 (65 to 89)

DaT-SPECT: dopamine transporter imaging with single-photon emission computed tomography; NPV: negative predictive value; PPV: positive predictive value.

The purpose of the gaps tables (see Tables 10 and 11) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. As shown below, neither study included the target population, i.e., patients having no core clinical features but 1 or more suggestive features. Neither study described how patients were chosen for inclusion from those that were eligible patients.

Table 10. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Walker (2009)[36,]	4: Patients met clinical criteria for dementia with Lewy bodies or AD; diagnoses were not clinically uncertain		3: No comparison to clinical criteria alone		
Thomas (2017) [37,]	4: Patients met clinical criteria for				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
	dementia with Lewy bodies or AD; diagnoses were not clinically uncertain				

AD: Alzheimer disease.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[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 (true positives, true negatives, false positives, false negatives cannot be determined).

Table 11. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Walker (2009)[36,]	1: Criteria used to select from eligible patients unclear					2: Comparison to clinical criteria alone not reported
Thomas (2017) [37,]	1: Criteria used to select from eligible patients unclear					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Ti1ming 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] Data Completeness 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.

Studies with Clinical Diagnosis Reference Standard

As previously stated, clinical diagnosis as a reference standard is a major study limitation. However, the largest study to evaluate DaT-SPECT for dementia with Lewy bodies is the prospective, investigator-initiated, multicenter study by McKeith et al (2007).[33,] It reviewed 326 patients with a clinical diagnosis of probable (n=94) or possible (n=57) dementia with Lewy bodies or non-dementia with Lewy bodies (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 dementia with Lewy bodies, a mean specificity of 90.4% for excluding non-dementia with Lewy bodies 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.

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 dementia with Lewy bodies 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 were not considered meaningful health outcomes for this evidence review.[38,] 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.[39,] 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 dementia with Lewy bodies; while imaging affected patient management, these outcomes were not detailed with respect to specific diagnostic changes.[40,] Further, many (irrespective of the imaging results) were in the earliest phase of their disease process and did not require immediate treatment for symptoms.

Chain of Evidence

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

Section Summary: Clinically Uncertain Dementia With Lewy Bodies

Two studies have been published with postmortem neuropathologic examination as the reference standard. Neither study included the target population, i.e., patients having no core clinical features but 1 or more suggestive features. Neither study described how patients were chosen for inclusion from those that were eligible patients. Therefore, the clinical validity of the test has not been established so a chain of evidence cannot be constructed. No direct evidence of benefit is available.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

2018 Input

Clinical input was sought to help determine whether the use of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) in individuals with clinically uncertain Parkinson disease (PD) or clinically uncertain dementia with Lewy bodies would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses identified through specialty societies.

In individuals who have clinically uncertain PD who receive DaT-SPECT, clinical input supports that DaT-SPECT is clinically useful when a negative result on DaT-SPECT is used to inform treatment decisions by reducing or avoiding unnecessary dopaminergic therapy. Clinical input highlights 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 PD. Clinical input further supports that DaT-SPECT offers clinically valid diagnostic information about the presence or absence of functional loss in the dopamine system (i.e., nigrostriatal degeneration) and is clinically useful for clinically uncertain Parkinsonian syndrome when a negative result on DaT-SPECT is used to inform treatment decisions by reducing or avoiding unnecessary dopaminergic therapy.

In individuals who have clinically uncertain dementia with Lewy bodies who receive DaT-SPECT, clinical input supports that DaT-SPECT is clinically useful when a positive result on DaT-SPECT is used to inform treatment decisions by avoiding potentially harmful use of neuroleptics which may be used in dementia patients. Clinical input noted that DaT-SPECT offers clinically valid diagnostic information about the presence or absence of functional loss in the dopamine system (i.e., nigrostriatal degeneration) and is clinically useful for clinically uncertain dementia with Lewy bodies 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.

Further details from clinical input are included in the Appendix.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology

The practice parameters from the American Academy of Neurology (2006; reaffirmed 2013; retired 2018) stated that β-CIT (2β-carbomethoxy-3β-(4-iodophenyl) tropane) and IBZM (iodobenzamide) SPECT are possibly useful in distinguishing PD from essential tremor (5 class III studies).[41,] There was insufficient evidence to determine whether these modalities are useful in distinguishing PD from other forms of parkinsonism.

American College of Radiology

In 2019, the American College of Radiology updated the appropriateness criteria for movement disorders and neurodegenerative diseases.[42,] The College categorized Ioflupane SPECT/computed tomography (CT) as 'may be appropriate' for initial imaging of Parkinsonian syndrome. A strength of evidence rating was not given for this statement.

The American College of Radiology (2019) updated the appropriateness criteria for dementia.[43,] The College categorized Ioflupane SPECT or SPECT/CT brain as 'may be appropriate' for initial imaging for suspected dementia with Lewy bodies. A strength of evidence rating was not given for this statement.

Dementia of Lewy Bodies Consortium

In 2017, the Dementia of Lewy Bodies Consortium published clinical guidelines on diagnosis and management based on American expert opinion.[44,] The guidelines stated that reduced DaT uptake in basal ganglia demonstrated by SPECT is an indicative biomarker. As such, dementia with abnormal DaT-SPECT imaging would be classified as possible dementia with Lewy bodies. The presence of another core clinical feature (fluctuating cognition, recurrent visual hallucinations, rapid-eye-

movement sleep disorder, parkinsonism motor abnormalities) in addition to dementia and abnormal DaT-SPECT imaging would allow classification as probable dementia with Lewy bodies. It was noted that patients with autopsy-confirmed dementia with Lewy bodies may have normal DaT-SPECT imaging.

Movement Disorders Society

In 2015, the Movement Disorders Society (MDS) published diagnostic criteria for PD intended for use in clinical research but also commonly used to guide clinical diagnosis.[15,] The MDS considers the clinical expert opinion to be the criterion standard to diagnose PD and that diagnoses are usually made clinically without ancillary diagnostic testing. Methods that may become available as knowledge advances are diagnostic biochemical markers, anatomic neuroimaging, and methods to detect alpha-synuclein deposition. Normal functional neuroimaging of the presynaptic dopaminergic system, if performed, is listed as an absolute exclusion criterion for PD. MDS noted that, although dopaminergic neuroimaging can help to distinguish parkinsonism from PD mimics like essential tremor, "it does not qualify as a criterion for the differentiation of PD from other parkinsonian conditions like atypical parkinsonian syndromes." Normal functional neuroimaging of the presynaptic dopaminergic system is also listed as criteria for exclusion from diagnosis of PD in patients with early/de novo PD.[45,]

National Institute for Health and Care Excellence

In 2006, the NICE published guidance on the diagnosis and management of PD,[46,] which was updated in 2017.[47,48,] The 2006 guidance stated that iodine 123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (^{123}I-FP-CIT) SPECT should be considered for people with tremor where essential tremor cannot be clinically differentiated from parkinsonism (based on studies with a level of evidence 1a or 1b); this recommendation is continued in 2017 guidance. Also unchanged was the recommendation that ^{123}I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation (based on the level of evidence IV, expert opinion).

The NICE updated its 2016 guidance on dementia in 2018.[49,] It recommended that ^{123}I-FP-CIT SPECT be used to help establish the diagnosis in those with suspected DLB [dementia with Lewy bodies] if the diagnosis is uncertain.

Society of Nuclear Medicine and Molecular Imaging et al

In 2020, the Society of Nuclear Medicine and Imaging and the European Association of Nuclear Medicine published a joint practice guideline and procedure standard for dopaminergic imaging in Parkinsonian syndromes.[50,] The guideline indicated presynaptic dopaminergic imaging for "detecting loss of nigrostriatal dopaminergic neuron terminals of patients with parkinsonian syndromes, especially:

- To support the differential diagnosis between essential tremor and neurodegenerative parkinsonian syndromes. Note that presynaptic dopaminergic imaging is unable to distinguish IPD [idiopathic Parkinson disease] and DLB from PSP [progressive supranuclear palsy], CBD [corticobasal degeneration], or putaminal variant of MSA [multiple system atrophy];
- To help distinguish between dementia with Lewy bodies and other dementias (in particular, Alzheimer's disease, AD);
- To support the differential diagnosis between parkinsonism due to presynaptic degenerative dopamine deficiency and other forms of parkinsonism, e.g., between IPD and drug-induced, psychogenic, or vascular parkinsonism;
- To detect early presynaptic parkinsonian syndromes."

In 2011, the Society of Nuclear Medicine, now called the Society of Nuclear Medicine and Molecular Imaging, provided practice guidelines for DaT-SPECT.[51,] The guidelines stated that the main indication for DaT-SPECT is striatal DaT visualization in the evaluation of adults with suspected parkinsonian syndromes to help differentiate essential tremor from tremor due to presynaptic

parkinsonian syndromes (PD, multisystem atrophy, progressive supranuclear palsy). Other indications are the early diagnosis of presynaptic parkinsonian syndromes, differentiation of presynaptic parkinsonian syndromes from parkinsonism without a presynaptic dopaminergic loss (e.g., drug-induced parkinsonism, psychogenic parkinsonism), and differentiation of dementia with Lewy bodies from AD. The guidance stated that visual interpretation of the scan is usually sufficient for clinical evaluation, where the striatal shape, extent, symmetry, and intensity differentiate normal from abnormal. For semiquantitative analysis, each site should establish its own reference range by scanning a population of healthy controls or by calibrating its procedure with another center that has a reference database.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 12.

Table 12. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01453127	DaTSCAN Imaging in Aging and Neurodegenerative Disease	500	Dec 2023
NCT02305147	Cohort Study to Identify Predictor Factors of Onset and Progression of Parkinson's Disease (ICEBERG)	360	Nov 2024
Unpublished			
NCT04193527[a]	A Multicentre, Phase 3, Clinical Study to Compare the Striatal Uptake of a Dopamine Transporter Radioligand, DaTSCAN™ Ioflupane (123I) Injection, After Intravenous Administration to Chinese Patients With a Diagnosis of Parkinson's Disease, Multiple System Atrophy, Progressive Supranuclear Palsy, or Essential Tremor and to Healthy Controls	172	Dec 2021

NCT: national clinical trial.
[a] Denotes industry sponsored or co-sponsored trial

Appendix 1

Appendix 1. 2018 Clinical Input
Clinical Input Objective
In 2018, clinical input was sought to help determine whether the use of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) in individuals with clinically uncertain Parkinson disease or clinically uncertain dementia with Lewy bodies and would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

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

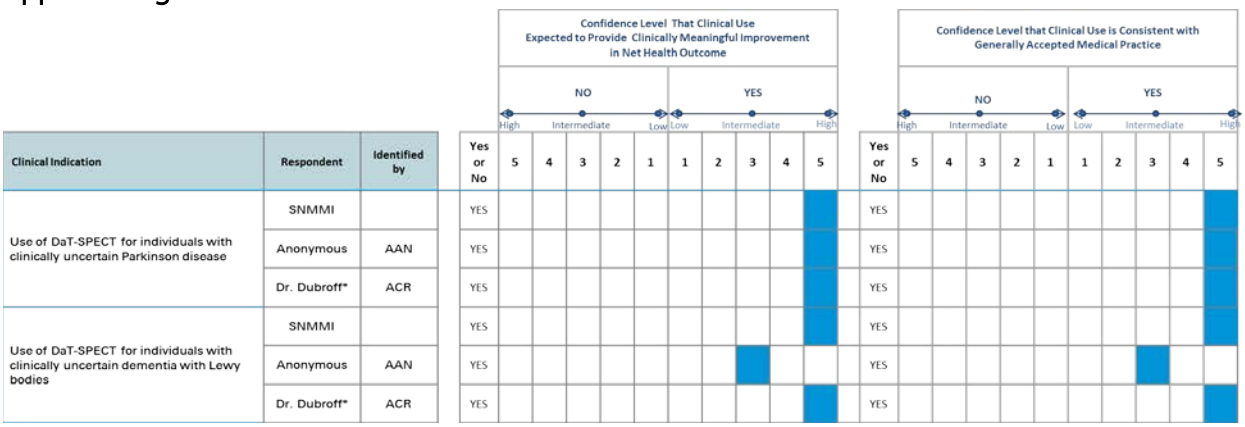
- Society of Nuclear Medicine and Molecular Imaging
- Anonymous, MD, Neurology, Movement Disorders, identified by American Academy of Neurology (AAN)
- Jacob G. Dubroff, MD, PhD, Nuclear Medicine, Assistant Professor of Radiology, University of Pennsylvania, identified by American College of Radiology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

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

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

Clinical Input Responses

Appendix Figure 1:



AAN: American Academy of Neurology; ACR: American College of Radiology; SNMMI: Society of Nuclear Medicine and Molecular Imaging.

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

Appendix Table 1. Respondent Profile

	Specialty Society				
No.	**Name of Organization**			**Clinical Specialty**	
1	Society of Nuclear Medicine and Molecular Imaging			Nuclear medicine	
	Physician				
No.	**Name**	**Degree**	**Institutional Affiliation**	**Clinical Specialty**	**Board Certification and Fellowship Training**
Identified by American Academy of Neurology					
2	Anonymous	MD		Neurology, movement disorders	American Board of Psychology and Neurology, Neurology; Movement Disorders Fellowship
Identified by American College of Radiology					
3	Jacob G. Dubroff	MD, PhD	Assistant Professor of Radiology, University of Pennsylvania	Nuclear medicine	American Board of Nuclear Medicine

Appendix Table 2. Respondent Conflict of Interest Disclosure

No.	1. Research support related to the topic where clinical input is being sought		2. Positions, paid or unpaid, related to the topic where clinical input is being sought		3. Reportable, more than $1000, healthcare-related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4. Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	Yes/No	Explanation	Yes/No	Explanation	Yes/No	Explanation	Yes/No	Explanation
1	No		No		No		No	
2	No		No		No		No	
3	No		Yes	I am currently involved in the joint European Association of Nuclear Medicine/Society of Nuclear Medicine and Molecular Imaging effort to develop procedural guidelines for dopaminergic imaging in Parkinsonian syndromes. I am not being paid for my participation.	No		No	

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.

Clinical Input Responses

Responses

1. Based on the evidence and your clinical experience, describe for each clinical indication listed below the narrative rationale that includes: (1) relevant authoritative scientific evidence and/or relevant clinical scenarios (e.g., a chain of evidence) supporting that use of the technology provides clinical meaningful improvement in net health outcome; and (2) any relevant patient inclusion or exclusion criteria or clinical context important to achieve a clinically meaningful improvement in net health outcome. Please include the PMID for any relevant references.
    a. Use of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) for individuals with clinically uncertain Parkinson disease (PD).

No.	Rationale
1	DAT SPECT imaging using 123I-FP-CIT SPECT (or 123I-ioflupane; DaTSCAN) is a very sensitive imaging technique to detect nigrostriatal degeneration in PD, even in preclinical phases (e.g., PMID: 28833467). Studies in clinically uncertain parkinsonian syndromes (CUPS) also showed its clinical validity (e.g., PMID: 19117369). Studies that examined the clinical validity of this technique in CUPS used clinical follow-up data as the reference test. In the literature on clinical validity of this test, post-mortem histopathology correlation is rarely used. However, other DAT SPECT tracers, and particularly 123I-beta-CIT (comparable to FP-CIT also from a chemical point of view) used this approach (e.g., PMID: 25048738). Since head-to-head studies showed comparable results between both tracers (i.e., same accuracy to detect loss of striatal DAT binding; e.g., PMID: 9044880), data of beta-CIT SPECT studies may be relevant to take also into account when addressing the clinical validity and utility of 123I-FP-CIT SPECT. In this regard, studies on SWEDD performed with beta-CIT SPECT may be of relevance to predict the accuracy of 123I-FP-CIT SPECT on this topic (e.g., PMID: 24759846). Nevertheless, there is need for more studies in SWEDD, as well as studies in CUPS with post-mortem confirmation. **References**

No.	Rationale
	• Iranzo A, Santamaria J, Valldeoriola F, et al. Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic rapid eye movement sleep behavior disorder. Ann Neurol. Sep 2017;82(3):419-428. PMID 28833467 • Marshall VL, Reininger CB, Marquardt M, et al. Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [123I]FP-CIT SPECT. Mov Disord. Mar 15 2009;24(4):500-8. PMID 19117369 • Kraemmer J, Kovacs GG, Perju-Dumbrava L, et al. Correlation of striatal dopamine transporter imaging with post mortem substantia nigra cell counts. Mov Disord. Dec 2014;29(14):1767-73. PMID 25048738 • Booij J, Tissingh G, Winogrodzka A, et al. Practical benefit of [123I]FP-CIT SPET in the demonstration of the dopaminergic deficit in Parkinson's disease. Eur J Nucl Med. Jan 1997;24(1):68-71. PMID 9044880 • Marek K, Seibyl J, Eberly S, et al. Longitudinal follow-up of SWEDD subjects in the PRECEPT Study. Neurology. May 20 2014; 82(20):1791-7. PMID 24759846
2	The DaTSPECT (DAT) scan test should not be considered a test for Parkinson's disease (PD). It is a test which effectively assesses the functional involvement of the striatal dopamine system. As such, the test, most effectively tests whether the dopamine system has been affected or not The test should only be used after a neurologist has established the clinical possibility (differential diagnosis) of any one of the neurodegenerative syndromes (PD, PSP, CBD, DLB, and others) with a differential diagnoses being a nonneurodegenerative syndrome (drug-induced parki[n]sonism, vascular parkinsonism, essential tremor). The practical clinical utility of the test is that, if normal, the result effectively makes it highly unlikely that any of the neurodegenerative set of diagnoses are present. In clinical practice, the negative DAT scan can change management by indicating a reduction in intensity of empiric dopaminergic medication use and relieve significant anxiety over the possibility of a neurodegenerative syndrome (which can be speculated to reduce health care utilization or phone calls/patient visits to multiple physicians in that subpopulation of patients). While the chain of evidence being sought is not definitive, there is clear evidence that appropriate selection of DAT scanning for uncertain syndromes (particularly distinguishing drug induced vs vascular parkinsonism as in Bega et al 2015) can change clinical management. There is the Kupsch 2012 study looking at health outcomes which had its flaws as in the review provided. In the absence of definitely health outcomes and gold standard diagnostics, change in clinical management should be taken into consideration -- especially when, in neurology, there is no shortage of selected patients for which either anxiety over diagnosis is driving phone calls or patients who are invested in a clinical PD diagnosis who are taking medications with potential for side-effects. In these cases, the utility of a negative DAT scan can provide immense benefit to patient-care and justifiable support for the physician to actively work to reduce medication risks. **References** • Bega D, Gonzalez-Latapi P, Zadikoff C, et al. Is there a role for DAT-SPECT Imaging in a specialty movement disorders practice? Neurodegener Dis. Jan 2015;15(2):81-86. PMID 25592727 • Kupsch AR, Bajaj N, Weiland F, et al. Impact of DaTscan SPECT imaging on clinical management, diagnosis, confidence of diagnosis, quality of life, health resource use and safety in patients with clinically uncertain parkinsonian syndromes: a prospective 1-year follow-up of an open-label controlled study. J Neurol Neurosurg Psychiatry. Jun 2012;83(6):620-628. PMID 22492213
3	PD is a chronic disease that often progresses insidiously, leaving significant diagnostic uncertainty. Therefore, the time-course of clinical meaningful improvement should be carefully considered. I-123 Ioflupane SPECT brain imaging (aka I-123 FP-CIT, DaTscan) is a safe, noninvasive, FDA approved, highly sensitive nuclear medicine imaging technique (PMID24947061) that identifies loss of striatal dopaminergic neurons, a known manifestation of PD, that has consistently demonstrated to have significantly superior accuracy to physical diagnosis alone (PMID 22492213,19117369). It has shown to be particularly useful in the setting of diagnostic uncertainty (PMID 25592727). Clinically meaningful outcome can be interpreted in several ways. First, using appropriate agents earlier on in the disease course to support a higher quality of life (e.g. dopaminergic therapy including L-Dopa, dopamine agonists like pramipexole, MAO-B inhibitors like selegiline, anticholinergics like benztropine, and amant[a]dine). Second, avoiding other medications that could exacerbate dopaminergic loss (e.g. antipsychotics) or removing medications (Drug Induced Parkinsonism) which could be causing the observed symptoms (PMID 15889951). Finally, the benefit of diagnostic confidence is under-valued and under-explored as optimizing the ability of a patient and family to plan and anticipate the course this disease is implicit in light of its mean 8-10 year survival from the time of diagnosis (PMID 18362281, 19224612). That is having greater diagnostic certainty and knowing sooner

No.	Rationale
	help both doctor and patient (including families) best manage this devastating disease better. **References** • Grosset DG, Tatsch K, Oertel WH, et al. Safety analysis of 10 clinical trials and for 13 years after first approval of ioflupane 123I injection (DaTscan). J Nucl Med. Aug 2014; 55(8):1281-7. PMID 24947061 • Kupsch AR, Bajaj N, Weiland F, et al. Impact of DaTscan SPECT imaging on clinical management, diagnosis, confidence of diagnosis, quality of life, health resource use and safety in patients with clinically uncertain parkinsonian syndromes: a prospective 1-year follow-up of an open-label controlled study. J Neurol Neurosurg Psychiatry. Jun 2012;83(6):620-8. PMID 22492213 • Marshall VL, Reininger CB, Marquardt M, et al. Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [123I]FP-CIT SPECT. Mov Disord. Mar 15 2009;24(4):500-8. PMID 19117369 • Bega D, Gonzalez-Latapi P, Zadikoff C, et al. Is there a role for DAT-SPECT Imaging in a specialty movement disorders practice? Neurodegener Dis. Jan 2015;15(2):81-86. PMID 25592727 • Aarsland D, Perry R, Larsen JP, et al. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry. May 2005;66(5):633-7.PMID 15889951 • Buter TC, van den Hout A, Matthews FE, et al. Dementia and survival in Parkinson disease: a 12-year population study. Neurology. Mar 25 2008;70(13):1017-22. PMID 18362281 • Diem-Zangerl A, Seppi K, Wenning GK, et al. Mortality in Parkinson's disease: a 20-year follow-up study. Mov Disord. 2009 Apr 30;24(6):819-25. PMID 19224612

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

No.	Rationale
1	DLB is the second most common type of dementia, but its diagnosis is challenging due to lack of widespread clinical expertise in making this diagnosis and variable presentation overlapping with PD and other non-parkinsonian syndromes. Behavioral therapies, physical therapy and medications have the greatest benefit if the diagnosis is made early. In addition, therapies targeted for Alzheimer's diseases, if used for patients with PD, can result in severe and sometimes life-threatening side effects. Therefore, appropriate diagnosis of PD is paramount in avoiding these complications.
2	The main use for DAT scans in clinically uncertain DLB in dementia clinics is the identification of patients with early hallucinations for whom a neuroleptic treatment is being considered. In most cases of early dementia, if there is a typical AD (Alzheimer's) type dementia with no red flags of early hallucinations or soft parkinsonism signs, neuroleptics are often used and escalated in potency. However, when there are some suggestions of parkinsonism or early hallucinations (criteria to consider DLB), the key consideration is whether a DAT scan can be used to highlight the distinction between those who should not receive neuroleptics (DLB) vs those who often do receive neuroleptics (AD). In clinically uncertain DLB, if the decision to escalate or use neuroleptics that are more risky (i.e. atypicals such as quetiapine are not helpful), a DAT scan may be used to ensure that emp[i]ric use of a more typical (and potent) neuroleptic is not given to a DLB patient with devastating consequences. In practice, the issue is that neuroleptics are often empirically used and escalated in dementia patients. If a[n] excessive (and sometimes fatal) neuroleptic reaction occurs, the retrospective diagnosis of DLB is made, and only after excessive health care costs of hospitalization may have been incurred. The empiric and ideal study that would study if DAT scan can identify patients before such patients receive neuroleptics beyond quetiapine has not yet been done. We note that the review provided comments that "DaT-SPECT has lower sensitivity and higher specificity than expert clinical diagnosis in patients with likely dementia with Lewy bodies." This statement should be noted that it may be confounded by the fact that diagnoses are often made with the criteria of neuroleptic sensitivity has been demon[s]trated already (as part of diagnostic criteria) at which point the clinical utility of a DAT scan is much less, even in patients early in disease process.
3	Like PD, DLB is a chronic progressive disease that can be challenging to diagnose because of its insidious onset. Also similar to PD, there is demise of the of the nigrostriatal dopaminergic brain circuity for which I-123 Ioflupane SPECT brain imaging has outstanding sensitivity (PMID 14531044, 16237129, 19300562, 17353255, 25632881). Specifically, DLB's non-specific cognitive and behavioral symptoms can mimic those also observed in Alzheimer's disease (AD), the most common neurodegenerative disease. I-123 Ioflupane SPECT has demonstrated excellent ability to detect the dopaminergic loss seen in DLB in order to distinguish it from AD (PMID 14531044). This is unlike emerging PET amyloid imaging which

No.	Rationale
	discern DLB from AD because amyloid is often present in DLB (PMID 25988463). There is also compelling evidence demonstrating that I-123 Ioflupane SPECT brain imaging predicts post-mortem DLB pathology and distinguish it from AD (PMID 27940650, 22961551, 17353255). Mean survival after DLB diagnosis has been estimated to be 8 years (PMID 27725535), similar to PD. This is important as an estimated 50% of DLB patients have a dangerous sensitivity to commonly used neuroleptic drugs including haldol (PMID 16237129). Exposure can often be fatal (PMID 27068351). Thus, avoidance of such medications is of paramount importance. **References** • Cost DC, Walker Z, Walker RW, et al. Dementia with Lewy bodies versus Alzheimer's disease: role of dopamine transporter imaging. Mov Disord. Oct 2003;18 Suppl 7:S34-8. PMID 14531044 • McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. Dec 27 2005;65(12):1863-72. Epub 2005 Oct 19. PMID 16237129 • Antonini A. The role of I-ioflupane SPECT dopamine transporter imaging in the diagnosis and treatment of patients with dementia with Lewy bodies. Neuropsychiatr Dis Treat. Jun 2007;3(3):287-92. PMID 19300562 • Walker Z, Jaros E, Walker RW, et al. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. J Neurol Neurosurg Psychiatry. Nov 2007;78(11):1176-81. Epub 2007 Mar 12. PMID 17353255 • McCleery J, Morgan S, Bradley KM, et al. Dopamine transporter imaging for the diagnosis of dementia with Lewy bodies. Cochrane Database Syst Rev. 2015 Jan 30;1:CD010633. PMID 25632881 • Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA. May 19 2015;313(19):1939-49. PMID 25988463 • Thomas AJ, Attems J, Colloby SJ, et al. Autopsy validation of 123I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB. Neurology. Jan 17 2017;88(3):276-283. PMID 27940650 • Colloby SJ, McParland S, O'Brien JT, et al.Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias. Brain. Sep 2012;135(Pt 9):2798-808. PMID 22961551 • Walker Z, Jaros E, Walker RW, et al.Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. J Neurol Neurosurg Psychiatry. Nov 2007;78(11):1176-81. PMID 17353255 • Manabe T, Mizukami K, Akatsu H, et al. Prognostic Factors Related to Dementia with Lewy Bodies Complicated with Pneumonia: An Autopsy Study. Intern Med. 2016;55(19):2771-2776. PMID 27725535 • Bonanni L, DiGiacomo R, D'Amico A, et al. Akinetic crisis in dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. Oct 2016;87(10):1123-6. PMID 27068351

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

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Use of DaT-SPECT for individuals with clinically uncertain PD	Yes					X
	Use of DaT-SPECT for individuals with clinically uncertain DLB	Yes					X
2	Use of DaT-SPECT for individuals with clinically uncertain PD	Yes					X
	Use of DaT-SPECT for individuals with clinically uncertain DLB	Yes			X		

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
3	Use of DaT-SPECT for individuals with clinically uncertain PD	Yes			X
	Use of DaT-SPECT for individuals with clinically uncertain DLB	Yes			X

3. Based on the evidence and your clinical experience for each of the clinical indications described in Question 1a and 1b:
   a. Respond Yes or No for each clinical indication whether this intervention is consistent with generally accepted medical practice; AND
   b. Rate your level of confidence in your Yes or No response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Use of DaT-SPECT for individuals with clinically uncertain PD	Yes					X
	Use of DaT-SPECT for individuals with clinically uncertain DLB	Yes					X
2	Use of DaT-SPECT for individuals with clinically uncertain PD	Yes					X
	Use of DaT-SPECT for individuals with clinically uncertain DLB	Yes			X		
3	Use of DaT-SPECT for individuals with clinically uncertain PD	Yes					X
	Use of DaT-SPECT for individuals with clinically uncertain DLB	Yes					X

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

No.	Response
1	Regarding technical utility, without doubt, the intra- and inter-variability for the assessment of 123I-FP-CIT SPECT scans is high (e.g., PMID: 24925885). However, also the test-retest reproducibility of the test itself is high (e.g., PMID: 9829575).The inclusion criteria, to examine the clinical utility of the tests, are very strict. Following these criteria, indeed, only one RCT examined the relationship between 123I-FP-CIT SPECT and health outcome in CUPS (PMID: 22492213). Although no significant differences in total score for QoL (PDQ-39) or health resource use were observed between groups during the 1-year follow-up period, the authors also described more management changes (including changes in diagnosis) in the imaging arm vs the non-imaging arm. The prognosis of parkinsonian syndromes with degeneration is worse than that for syndromes without degeneration. This is e.g., reflected by the observation that during this study there were 7 hospitalizations in the imaging arm, and all had an abnormal scan. So one may take this also into account when examining the clinical utility. PD is slowly progressive, and when QoL questionnaires like the PDQ-39 are used to measure QoL, longer follow-up data are needed (or larger studies) to show significant changes in relation to DAT imaging. Also, other studies showed that the technique is cost-effective (PMID: 18385998; PMID: 18785639). Finally, export reports support the use of 123I-FP-CIT in CUPS (e.g., PMID: 27813429). Therefore, appropriate diagnosis and timely intervention will provide a clinically meaningful improvement

No.	Response
	in net health outcome of parkinsonian syndromes. **References** • Seibyl JP, Kupsch A, Booij J, et al. Individual-reader diagnostic performance and between-reader agreement in assessment of subjects with Parkinsonian syndrome or dementia using 123I-ioflupane injection (DaTscan) imaging. J Nucl Med. Aug 2014;55(8):1288-96. PMID 24925885 • Booij J, Habraken JB, Bergmans P, et al. Imaging of dopamine transporters with iodine-123-FP-CIT SPECT in healthy controls and patients with Parkinson's disease. J Nucl Med. Nov 1998;39(11):1879-84. PMID 9829575 • Kupsch AR, Bajaj N, Weiland F, et al. Impact of DaTscan SPECT imaging on clinical management, diagnosis, confidence of diagnosis, quality of life, health resource use and safety in patients with clinically uncertain parkinsonian syndromes: a prospective 1-year follow-up of an open-label controlled study. J Neurol Neurosurg Psychiatry. Jun 2012;83(6):620-8. PMID 22492213 • Van Laere K, Everaert L, Annemans L, et al. The cost effectiveness of 123I-FP-CIT SPECT imaging in patients with an uncertain clinical diagnosis of parkinsonism.Eur J Nucl Med Mol Imaging. Jul 2008;35(7):1367-76. PMID 18385998 • Antonini A, Berto P, Lopatriello S, et al. Cost-effectiveness of 123I-FP-CIT SPECT in the differential diagnosis of essential tremor and Parkinson's disease in Italy. Mov Disord. Nov 15 2008;23(15):2202-9. PMID 18785639 • Isaacson SH, Fisher S, Gupta F, et al. Clinical utility of DaTscan™ imaging in the evaluation of patients with parkinsonism: a US perspective. Expert Rev Neurother. Mar 2017;17(3):219-225. PMID 27813429
2	a. For patients who have PD --> empiric tx is standard of care b. For patients who do not actually have PD, empiric treatment puts patients at risk for side effects of sedation, lightheadedness, hallucinations, vivid dreams, agitation that is not necessary. c. Patients with atypical parkinsonism carry greater risk for all side effects of empiric treatment with limited benefit. d. Patients with dystonia (not parkinsonism) are often treated with parkinsonism empirically for which DAT scanning is not indicated and a subgroup (dopa-responsive dystonia), the treatment is critical to their well-being.
3	These questions are best answered by Neurologists who sub-specialize in the diagnosis and treatment of movement disorders. However, the risk of using neuroleptic drugs in PD patients is noted (PMID 12735915,15889951). **References** • Ikebe S, Harada T, Hashimoto T, et al. Prevention and treatment of malignant syndrome in Parkinson's disease: a consensus statement of the malignant syndrome research group. Parkinsonism Relat Disord. Apr 2003;9 Suppl 1: S47-9. PMID 12735915 • Aarsland D, Perry R, Larsen JP, et al. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry. May 2005;66(5):633-7. PMID 15889951

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

No.	Response
1	We believe that these questions should be answered by movement disorder specialists.
2	a. no issue with empiric follow-up b. for patients who do not have PD but are concerned about PD (and generate a lot of patient visits, phone calls, anxiety), the DAT scan is an essential clinically appropriate test to assess the dopaminergic system. When normal, it allows a confirmation that they do not have PD (or other neurodegenerative diagnosis that affects the dopamine system), and clarifies appropriate

No.	Response
	treatment which involves reduction of or cautious use of PD treatments if at all. This is the primary clinical indication I find most helpful. c. active follow-up for parkinsonism is usually reasonable. If a patient with PD is very against taking PD medications (and perhaps due to denial of diagnosis), in that particular circumstance, when it is clearly clinically indicated to provide treatment of symptoms affecting patient's function or livelihood, a DAT scan, if presented appropriately, can be used address the denial of diagnosis aspect of care. This is not anticipated to come up much at all (has occurred perhaps 1-2 times over 10 years) d. not particularly.
3	These questions are best answered by Neurologists who sub-specialize in the diagnosis and treatment of movement disorders. However, the risk of using neuroleptic drugs in PD patients is noted (PMID 12735915,15889951). **References** • Ikebe S, Harada T, Hashimoto T, et al. Prevention and treatment of malignant syndrome in Parkinson's disease: a consensus statement of the malignant syndrome research group. Parkinsonism Relat Disord. Apr 2003;9 Suppl 1: S47-9. PMID 12735915 • Aarsland D, Perry R, Larsen JP, et al. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry. May 2005;66(5):633-7. PMID 15889951

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

No.	Response
1	We believe that these questions should be answered by movement disorder specialists.
2	a. decision for treatment for those who have clinical PD is a clinical decision. It does not depend on a DAT scan b. decision for treatment for those who do NOT have PD but are being treated for PD is the primary clinical indication for accurate imaging. Accurate imaging reflects state of the dopaminergic system and if normal, it is highly unlikely the patient has a neurodegenerative syndrome such as PD. This will encourage surveillance and holding off on treatment.
3	These questions are also best answered by a Neurology movement disorder specialist.

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

No.	Response
1	We believe that these questions should be answered by movement disorder specialists.
2	No comment.
3	Yes, this is the appropriate reference standard (Rizzo et al. 2016) • Rizzo G, Copetti M, Arcuti S, et al. Accuracy of clinical diagnosis of Parkinson disease: A systematic review and meta-analysis. Neurology. Feb 09 2016;86(6):566-576. PMID 26764028

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

No.	Additional Comments
1	Both biochemical and imaging biomarkers are increasingly being incorporated into clinical practice. SPECT imaging with DaTScan is a very good example of the biomarker with a great clinical value as it is capable

No.	Additional Comments
	of differentiating non Parkinsonian syndromes which can have similar clinical presentation as Parkinsonian syndromes.
2	No response
3	There are three issues regarding the included evidence summary of I-123 Ioflupane SPECT brain imaging for diagnosis of PD or DLB. First, correlation between I-123 Ioflupane studies and post-mortem tissue as demonstrating the validity of the test are not included (PMID 27940650, 22961551, 17353255). Second, the potential fatal dangers of neuroleptic malignant syndrome in both DLB and PD are under-emphasized (PMID 12735915,15889951) as poor outcomes that could nearly impossible to evaluate from an ethical perspective using a prospective trial. Finally, in the "Technical Reliability", there is the following uncited statement: "Dopamine agonists and levodopa may also affect DaT expression, which could influence the ability of DaT-SPECT to monitor progression of disease." There is evidence to the CONTRARY (PMID 16151764). Specific medications that bind the molecular target (presynaptic dopamine transporter) of I-123 Ioflupane imaging and could possibly interfere with the study are known and avoided prior to the study (PMID 20019219). This is an great reference that was not included (PMID 24947061).**References** • Thomas AJ, Attems J, Colloby SJ, et al. Autopsy validation of 123I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB. Neurology. Jan 17 2017;88(3):276-283. PMID 27940650 • Colloby SJ, McParland S, O'Brien JT, et al.Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias. Brain. Sep 2012;135(Pt 9):2798-808. PMID 22961551 • Walker Z, Jaros E, Walker RW, et al. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single-photon emission computed tomography imaging and autopsy. J Neurol Neurosurg Psychiatry. Nov 2007;78(11):1176-81. Epub 2007 Mar 12. PMID 17353255 • Ikebe S, Harada T, Hashimoto T, et al. Prevention and treatment of malignant syndrome in Parkinson's disease: a consensus statement of the malignant syndrome research group. Parkinsonism Relat Disord. Apr 2003;9 Suppl 1: S47-9. PMID 12735915 • Aarsland D, Perry R, Larsen JP, et al. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry. May 2005;66(5):633-7. PMID 15889951 • Schillaci O, Pierantozzi M, Filippi L, et al. The effect of levodopa therapy on dopamine transporter SPECT imaging with(123)I-FP-CIT in patients with Parkinson's disease. Eur J Nucl Med Mol Imaging. Dec 2005;32(12):1452-6. PMID 16151764 • Kägi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. J Neurol Neurosurg Psychiatry. Jan 2010;81(1):5-12. PMID 20019219 • Grosset DG, Tatsch K, Oertel WH, et al. Safety analysis of 10 clinical trials and for 13 years after first approval of ioflupane 123I injection (DaTscan). J Nucl Med. Aug 2014;55(8):1281-7. PMID 24947061

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

No.	Yes/No	Citations of Missing Evidence
1	No	
2	No	
3	Yes	This is summarized in question 8.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Reason for DAT-SPECT
  - Previous Imaging reports (e.g., CT, MRI, SPECT)
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)

Post Service (in addition to the above, please include the following):

- DAT-SPECT report

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	78803	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT), single area (e.g., head, neck, chest, pelvis) or acquisition, single day imaging
HCPCS	A9584	Iodine I-123 ioflupane, diagnostic, per study dose, up to 5 mCi

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/28/2013	BCBSA Medical Policy adoption
09/30/2014	Policy title change from Dopamine Transporter Imaging with Single Photon Emission Computed Tomography (DAT-SPECT) Policy revision without position change
04/01/2016	Policy title change from Dopamine Transporter Imaging with Single Photon Emission Computed Tomography Policy revision without position change
11/01/2016	Policy revision without position change
12/01/2017	Policy revision without position change
12/01/2018	Policy revision without position change
05/01/2019	Policy revision with position change
12/01/2019	Policy revision without position change
01/01/2024	Policy title changed from Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography to current one. Policy reactivated. Previously archived from 08/01/2020 to 12/31/2023.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Dopamine Transporter Single-Photon Emission Computed Tomography 6.01.54** **Policy Statement:** I. Dopamine transporter imaging with single-photon emission computed tomography may be considered **medically necessary** when used for individuals with: A. Clinically uncertain Parkinson disease B. Clinically uncertain dementia with Lewy bodies II. Use of dopamine transporter imaging with single-photon emission computed tomography is considered **investigational** for all other indications not included above.