Medical Policy

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***Current Policy Effective Date: 7/1/23**
(See policy history boxes for previous effective dates)

Title: Dopamine Transporter Imaging with Single Photon Emission Computed Tomography (DaTscan™)

Description/Background

Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), using radiopharmaceutical ioflupane (^{123}I) injection, is a neuro-imaging modality being evaluated to improve the differential diagnosis of parkinsonian syndromes from nonparkinsonian tremor, as well as dementia with Lewy bodies from Alzheimer disease.

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

Diagnosis can be challenging, particularly when patients have multiple comorbidities including

cerebrovascular disease and/or Alzheimer disease.(1) As with PD, DLB is characterized by the degeneration of nigrostriatal neurons; as such, DaT-SPECT is also proposed to differentiate DLB from Alzheimer disease.

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.

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

Binding of ligands with affinity for dopamine transporter ligands in the striatum is, in general, reduced in Parkinson disease (PD), genetic parkinsonism, dementia with Lewy bodies (DLB), corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy. In contrast, striatal DaT ligand binding is expected to be within the normal range in Alzheimer disease, essential tremor, dystonic tremor, orthostatic tremor, drug-induced parkinsonism, psychogenic parkinsonism, and vascular parkinsonism.(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, DLB, or other neurodegenerative parkinsonian syndrome, while a normal DaT-SPECT scan in a symptomatic patient supports the diagnosis of a disease not affecting the nigrostriatal dopaminergic pathway.

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

Anatomic variation in the brain, including vascular lesions, may interfere with 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 progression of disease unless these agents are discontinued prior to imaging. Patients with clinically diagnosed PD or DLB, who present with a normal DaT-SPECT scan, are referred to in the literature as having “scans without evidence of dopaminergic deficit.”. While many of these patients are ultimately diagnosed with non-PD syndromes, a portion of patients with normal DaT-SPECT imaging are confirmed to have PD or DLB by the reference standard. In studies

where clinical diagnosis is used as an end point, scans without evidence of dopaminergic deficit are present in 3% to 20% of PD patients.(11) In a study of patients clinically diagnosed with DLB, van der Zande et al (2016) found that 10% of these patients had normal scans.(12) Further research may shed light on these cases.

Regulatory Status

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

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

Medical Policy Statement

The safety and effectiveness of dopamine transporter imaging with single photon emission computed tomography have been established for patients meeting specified criteria. It may be considered a useful diagnostic option when specific clinical criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions:

- To aid in the diagnosis of a parkinsonian syndrome (e.g. essential tremor v. Parkinson's disease)
- To distinguish drug-induced parkinsonism (DIP) v. degenerative parkinsonism or idiopathic Parkinson's disease
- To discriminate psychogenic parkinsonism from neurologically-based parkinsonism
- To be used prior to DBS surgery for intractable tremor of uncertain etiology to determine the appropriate site of DBS stimulation (e.g. VIM stimulation for essential tremor v. STN or GPi stimulation for Parkinson's disease)
- To distinguish between dementia with Lewy bodies and Alzheimer disease
- DaTscan should only be ordered by a board-certified neurologist who has evaluated the patient

Exclusions:

- As a screening or confirmatory test and for monitoring disease progression or response to therapy
- Serial DaTscan studies

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

A9584 78803

Other codes (investigational, not medically necessary, etc.):

N/A

Note: The above code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

TESTING FOR CLINICALLY UNCERTAIN PARKINSON DISEASE

Clinical Context and Test Purpose

The purpose of dopamine transporter imaging with single-photon emission computed tomography (DaTSPECT) is to differentiate essential tremor from tremor due to parkinsonian syndromes in order to guide appropriate management decisions. Specifically, in patients for whom the diagnosis of ET versus 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 essential tremor (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 Parkinson Disease (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 question addressed in this evidence review is: In individuals or whom the diagnosis of ET versus PD is unclear after clinical evaluations, does the use of DaT-SPECT improve the net health outcome?

The following PICOs were 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 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 end point 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 (eg, those with essential tremor 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 (ie, tremor, slowness of movements, rigidity, instability), nonmotor symptoms (eg,

mood, fatigue, daytime sleepiness), and quality of life (eg, limitations in daily activities due to symptoms). Outcomes may also include treatment-related morbidity and mortality, particularly in regards to 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, 3.6-13.8 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 postmortemm 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 (eg, 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 1-4).

Studies of clinical validity for DaT-SPECT in diagnosing PD rely on the reference standard end point of diagnosis by a clinician, based on physical diagnosis and patient history; 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 essential tremor (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 (k range, 0.94-0.97). The baseline clinical diagnosis and reference standard end point was video analysis of the patient, at the start of the study and after 36 months, by movement disorder specialists who were blinded to imaging data and patient history. Comparison of the baseline DaT-SPECT scans with the reference standard end point revealed a sensitivity of 78% and specificity of 97%. Comparison of the baseline clinical diagnosis with the reference standard end point showed a sensitivity of 93% and specificity of 46%. Of the 71 patients with clinical diagnosis of parkinsonian syndrome (including PD, multiple system atrophy, and progressive supranuclear palsy) at the end of this study, 1 patient had a DaT-SPECT scan that changed from normal to abnormal between the baseline and the scan at 36 months, and 1 patient had a DaT-SPECT scan that changed from abnormal to normal in the same time. Both patients were clinically diagnosed with PD. Of note, 15 (21%) patients with a clinical diagnosis of PD had unexpectedly normal DaT-SPECT imaging at baseline, 18 months, and 36 months. It is not known whether these cases of scans without evidence of dopaminergic deficit resulted from a false-negative DaT-SPECT scan or an incorrect reference standard end point of clinical diagnosis. Strengths and weaknesses of this study are detailed in Tables 1, 3, and 4.

Vlaar et al (2008) retrospectively reviewed a population of patients with clinically uncertain PD, but the reference standard end point did not use clinicians blinded to DaT-SPECT scans.(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 DaTSPECT 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 • Met criteria for both PS and ET • UPDRS-III score ≤16	• Other potential causes of parkinsonism or tremor • Major comorbid illness • Iodine sensitivity	• Protocol violations • Personal reasons • Safety or medical reasons • Loss to follow-up
Kupsch et al (2012, 2013)[21.22] Hauser et al (2014)[23]	19 U.S. and European centers	• Clinically uncertain, monosymptomatic, atypical, or incomplete presentation with possible parkinsonian syndrome • Early-onset parkinsonian syndrome (<5 y of symptoms)	• Differential diagnosis of PD vs PSP or MSA • Diagnosed movement disorder or cause of tremor	• Protocol violations • Patient request • Loss to follow-up

Bajaj et al (2014)[24]		• Significant cognitive impairment • Medications known to interact with DaT-SPECT scan

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), %	NPV (95% CI), %
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) <0.001	96.8 (83.3 to 99.9) 0.002	98.2 (90.1 to 100) NR	66.2 (49.8 to 80.0) NR
Kupsch et al (2012, 2013)[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) 0.48	100 (91.2 to 100) 0.14	89.5 (66.9 to 98.7) 0.3

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 FU[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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
AE: adverse event; DaT-SPECT: dopamine transporter imaging with single-photon emission computed tomography; ET: essential tremor; FU: follow-up; PS: parkinsonian syndromes including Parkinson disease, multiple system atrophy, and progressive supranuclear palsy.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[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 FU 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)[21,22] 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	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
DAT-SPECT: dopamine transporter imaging with single-photon emission computed tomography; FU: follow-up.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[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 RCTs.

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

Kupsch et al (2012, 2013) reported on an open-label, multicenter randomized trial from 19 university hospital centers in Europe and the United States.(21,22) 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.(21-24) Patients were randomized to DaT-SPECT (n=109) or no imaging (n=123), with DaTSPECT imaging classified as normal or abnormal by a physician blinded to clinical history; they were then followed for 1 year by neurologists with (n=12) or without (n=7) movement disorder specialization. Health outcomes at 3 months after scan revealed no significant difference in the quality of life.(22) Again, health outcomes in the same population at 1 year after the scan showed no significant difference in the quality of life or health resource utilization between those who received a DaT-SPECT scan, and those who did not.(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 (NPV, PPV) of the DaT-SPECT test, relative to the reference standard, resulted in specific management changes that have been shown to improve health outcomes. Changes in medications alone are not sufficient to demonstrate improved health outcomes unless these changes are demonstrated to be applied correctly and beneficially in the target population. 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 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, who were given a final diagnosis of

parkinsonian syndrome. Change in clinical management was seen in 41 (63%) patients of whom 30 (73%) were either clinically stable or improved at follow-up. A subset of 10 patients was found to have drug-induced PD without any striatal neurodegeneration noted on DaT-SPECT scan; these patients were then advised to discontinue the drugs or reduce the doses of their drug intake. No follow-up information comparing DaT-SPECT with the reference standard (clinical diagnosis over sufficient time), which would validate treatment decisions, was provided. Specific health outcomes resulting from specific change in management were also not provided.

Oravivattanakul et al (2015) reported on a case series of patients with baseline diagnoses of neurodegenerative parkinsonism (including PD, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration; n=70), non-neurodegenerative parkinsonism (n=46), uncertain diagnosis (n=45), and ET (n=14).(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 DaTSPECT.(30) Patients were classified by diagnostic dilemma, including PD vs ET (n=18), PD vs drug-induced parkinsonism (n=18), or PD vs vascular parkinsonism (n=12). While the series detailed initiation, discontinuation, or escalation of medications for PD in these subpopulations, these changes in management were not linked to specific diagnostic decisions or DaT-SPECT results.

Several studies were excluded from this review because they lacked appropriate health outcome metrics, as described above. Two of them reviewed a prospective multicenter trial on the diagnostic and clinical management impact of DaT-SPECT on 118 patients with clinically uncertain parkinsonism syndrome;(31,32) while imaging changed diagnosis and management, neither study detailed these outcomes relative to specific diagnostic changes.

Section Summary: Clinically Uncertain Parkinson Disease

Evidence reported through clinical input augments the published evidence by outlining a chain of evidence how the use of DaT-SPECT informs management decisions that improve the net health outcome of care. For individuals with clinically uncertain PD, which includes unusual clinical features, incomplete or uncertain responsiveness to dopaminergic medication, or clinical diagnostic uncertainty after evaluation by a specialist, negative results on DaT-SPECT may be used to distinguish neurodegenerative parkinsonian syndromes involving functional loss of dopamine system (eg, Parkinson disease; progressive supranuclear palsy; corticobasal degeneration; multiple system atrophy; dementia with Lewy bodies) from conditions without functional loss of dopamine system (eg, essential tremor, drug-induced parkinsonism, or vascular parkinsonism). Use of DaT-SPECT to exclude functional loss of the dopamine system (i.e., nigrostriatal degeneration) may be clinically useful to inform treatment decisions by reducing or avoiding unnecessary dopaminergic therapy.

TESTING FOR CLINICALLY UNCERTAIN DEMENTIA WITH LEWY BODIES

Clinical Context and Test Purpose

The purpose of DaT-SPECT testing of individuals with uncertain dementia with Lewy bodies (DLB) is to establish the clinical diagnosis of DLB in order to guide appropriate management decisions.

Diagnosis of Dementia with Lewy Bodies

The Consortium on Dementia with Lewy Bodies has developed consensus criteria for the clinical diagnosis of DLB.(33) Clinical signs and symptoms of DLB 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 5-6 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 (eg, constipation, orthostatic hypotension, urinary incontinence)
	• 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 DLB	Two or more core clinical features of DLB are present, with or without indicative biomarkers; OR· Only one core clinical feature is present, but with one or more indicative biomarkers
Possible DLB	Only one core clinical feature of DLB is present, with no indicative biomarker evidence; OR· One or more indicative biomarkers are present, but there are no core clinical features
DLB 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 DLB that have been shown to have disease-modifying effects. Treatment of DLB is symptomatic. Nonpharmacologic and behavioral therapies may be used. Although the evidence of effectiveness is limited for DLB, 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 DLB, including exacerbation of parksinsonism, severe confusion, heavy sedation and even death.

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

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

Populations

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

Based on the diagnostic criteria shown in Table 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***
Patients with dementia having two or more *core* clinical features of DLB	Patient meets criteria for probable DLB without DaT-SPECT
Patients with dementia having only one *core* clinical feature	DaT-SPECT can aid in distinguishing between possible DLB and probable DLB
Patients with dementia having no *core* clinical features but one or more *suggestive* features	DaT-SPECT can aid in diagnosing possible DLB

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 dementiawith 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 tolead 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 physical exam and medical history.

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

Comparators
The criterion standard for the diagnosis of DLB is postmortem neuropathologic examination.

In the absence of comparisons with the criterion standard, diagnosis by expert clinicians may be used as a reference standard for diagnosis of DLB.

Outcomes
Health outcomes are defined as disease-related morbidity, functional outcomes, and treatment-related mortality and morbidity. Assessment of DLB may include tests such as the Lewy Body Composite Risk Score,(34) which assesses motor symptoms (ie, rigidity, postural instability) and non-motor symptoms (ie, daytime sleepiness, hallucinations). Assessment of DLB may also include general tests for dementia including the Clinical Dementia Rating test.

With the criterion standard of DLB (histopathology), diagnostic accuracy can only be confirmed after death.

The correct dementia clinical diagnosis may become more evident over time for some types of dementia. As DLB 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
- 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 (eg, 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 Clinical Diagnosis Reference Standard

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

Clinically Useful

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

Direct Evidence

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

The preferred RCT would evaluate health outcomes in patients with clinically uncertain DLB who received the new diagnostic test compared with patients who received the standard of care. Physician confidence, changes in diagnosis, and changes in management 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 diagnostic change and diagnostic confidence alone, which was not considered meaningful health outcomes for this evidence review.(35) 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.(36) Both studies were limited by a small population (N=114) and short follow-up (6 months). Finally, Kemp et al (2011) retrospectively evaluated 80 consecutive patients with DLB; while imaging affected patient management, these outcomes were not detailed with respect to specific diagnostic changes.(37) Further, many (irrespective of the imaging results) were in the earliest phase of their disease process and did not require immediate treatment for symptoms.

Chain of Evidence

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

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

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

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

For individuals who have clinically uncertain Parkinson disease who receive DaT-SPECT, the published evidence includes randomized controlled trials, cohort studies, and case series studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. In populations with clinically apparent Parkinson disease, studies of diagnostic accuracy have reported high sensitivity and specificity for Parkinson disease. Evidence reported through clinical input augments the published evidence by highlighting that the published RCT also reported changes in management following DaT-SPECT imaging that may translate to improvements in health outcomes over time, and the 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 Parkinson syndrome when a negative result on DaT-SPECT is used to inform treatment decisions by reducing or avoiding unnecessary dopaminergic therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have clinically uncertain dementia with Lewy bodies who receive DaT-SPECT, the published evidence includes randomized control trials, cohort studies, and case series studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related mortality and morbidity. Evidence reported through clinical input augments the published evidence by supporting that DaT-SPECT offers clinically valid diagnostic information about the presence or absence of functional loss in the dopamine system (i.e., nigrostriatal

degeneration) and is clinically useful for clinically uncertain DLB using a chain of evidence where a positive result on DaT-SPECT is used to inform treatment decisions by avoiding potentially harmful use of neuroleptics typically used in dementia patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials are listed in Table 8.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01453127	DaTSCAN Imaging in Aging and Neurodegenerative Disease	500	Dec 2022
NCT01141023	The Parkinson's Progression Markers Initiative (PPMI)	1100	Dec 2022
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	Sep 2020

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

Supplemental Information

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

2018 Input

In response to requests, clinical input on use of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) for diagnosing clinically uncertain Parkinson disease and clinically uncertain dementia with Lewy bodies was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses identified through specialty societies including physicians with academic medical center affiliations, while this policy was under review in 2018.

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 RCT 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 (ie, nigrostriatal degeneration) and is clinically useful for clinically

uncertain Parkinson syndrome when a negative result on DaT-SPECT is used to inform treatment decisions by reducing or avoiding unnecessary dopaminergic therapy.

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 DaTSPECT offers clinically valid diagnostic information about the presence or absence of functional loss in the dopamine system (ie, nigrostriatal degeneration) and is clinically useful for clinically uncertain 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.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Radiology and the American College of Nuclear Medicine

The ACR–ACNM (2017) published a practice parameter regarding the performance of DaT SPECT imaging for movement disorders.(49) The document states the following:

“Clinical indications for DaT SPECT imaging include, but are not limited to:
Differentiating Parkinsonian syndrome from essential tremor and drug-induced tremor in patients with:

1. Worsening essential tremor
2. Tremor who use neuroleptics
3. Tremor “who want to know”
4. Psychogenic factors
5. Dementia, to differentiate Alzheimer disease and dementia with Lewy bodies.”

American College of Radiology

In 2019, the American College of Radiology updated the appropriateness criteria for movement disorders and neurodegenerative diseases.(38) The College categorized Ioflupane SPECT/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.(39) The College categorized Ioflupane SPECT or SPECT/CT brain as 'may be appropriate' for initial imaging for suspected dementia with Lewy bodies.

American Academy of Neurology

The practice parameters from the American Academy of Neurology (2006; reaffirmed 2013) stated that β-CIT and IBZM (iodobenzamide) SPECT are possibly useful in distinguishing PD from essential tremor (5 class III studies).(40) There was insufficient evidence to determine whether these modalities are useful in distinguishing PD from other forms of parkinsonism.

Society of Nuclear Medicine and Molecular Imaging 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.(41) 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 [dementia with Lewy bodies] 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."

The Society of Nuclear Medicine, now called the Society of Nuclear Medicine and Molecular Imaging (2011), provided a practice guideline for DAT-SPECT.(42) The guidelines stated that the main indication for DAT-SPECT is striatal DAT visualization in the evaluation of adults with suspected parkinsonian syndrome (PD) to help differentiate essential tremor from tremor due to presynaptic parkinsonian syndrome (PD, multiple-system atrophy, progressive supranuclear palsy). Other indications are the early diagnosis of presynaptic parkinsonian syndrome (PS), differentiation of presynaptic PS from parkinsonism without presynaptic dopaminergic loss (eg, drug-induced parkinsonism, psychogenic parkinsonism), and differentiation of DLB from Alzheimer disease. The guidance stated that visual interpretation of the scan is usually sufficient for clinical evaluation, where the striatal shape, extent, symmetry, and intensity differentiate normal from abnormal. For semiquantitative analysis, each site should establish its own reference range by scanning a population of healthy controls or by calibrating its procedure with another center that has a reference database.

Movement Disorders Society

The Movement Disorder Society's (MDS; 2015) diagnostic criteria for PD from are intended for use in clinical research but CAN be used to guide clinical diagnosis.(16) MDS considers clinical expert opinion to be the criterion standard to diagnose PD and that diagnoses are usually made clinically without need for ancillary diagnostic testing. Methods that may become available as knowledge advances are diagnostic biochemical markers, anatomical neuroimaging, and methods to detect alpha-synuclein deposition. Normal functional neuroimaging of the presynaptic dopaminergic system, if performed, is listed as an absolute exclusion criteria for PD. MDS noted that, although dopaminergic neuroimaging can help to distinguish parkinsonism from PD mimics like ET, "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.(43)

European Federation of Neurological Societies and Movement Disorder Society

The European Federation of Neurological Societies and Movement Disorder Society–European Section (EFNS/MDS-ES) published recommendations for the diagnosis of PD in 2013.(50) EFNS/MDS-ES provided a level A recommendation for the use of DAT-SPECT in the differential diagnosis between degenerative parkinsonism and essential tremor. The guidelines specified that DAT-SPECT is indicated in the presence of significant diagnostic uncertainty and particularly in patients presenting atypical tremor manifestations.

European Association of Nuclear Medicine
The European Association of Nuclear Medicine's neuroimaging committee published updated guidelines on procedures for DAT-SPECT in 2010, based on the individual experience of experts in European countries.(51) The guidelines stated that iodine 123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (^{123}I-FP-CIT) imaging is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain parkinsonian syndrome and for the differentiation of DLB from other dementias. Other indications are the early diagnosis of neurodegenerative parkinsonism, assessment of disease severity, and differentiation of presynaptic parkinsonism from other forms of parkinsonism (eg, neuroleptic-induced parkinsonism). The guidelines stated that, in addition to visual interpretation, semiquantitative analysis is recommended to objectively assess striatal DAT binding. Issues requiring further clarification include the assessment of disease progression and effects of treatments and methods for operator-independent definition of region of interest.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (2006) published guidance on the diagnosis and management of PD,(44) which was updated in 2017.(44,45) The 2006 guidance stated that iodine 123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (123I-FP-CIT) SPEC should be considered for people with tremor where essential tremor cannot be clinically differentiated from parkinsonism (based on studies with level of evidence 1a or 1b); this recommendation is continued in 2017 guidance. Also unchanged was the recommendation and that ^{123}I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation (based on level of evidence IV, expert opinion).

The NICE updated its 2016 guidance on dementia in 2018.(47) It recommended that ^{123}I-FP-CIT SPECT be used to help establish the diagnosis in those with suspected DLB if the diagnosis is uncertain.

Dementia of Lewy Bodies Consortium
The Dementia of Lewy Bodies Consortium (2017) published clinical guidelines on diagnosis and management, based on American expert opinion.(48) The guidelines stated that reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT is an indicative biomarker. As such, dementia with abnormal DaT-SPECT imaging would be classified as possible DLB. The presence of another core clinical feature (fluctuating cognition, recurrent visual hallucinations, rapid eye movement sleep disorder, parkinsonism motor abnormalities) in addition to dementia and abnormal DaT-SPECT imaging would allow classification as probable DLB. It was noted that patients with autopsy-confirmed DLB may have normal DaT-SPECT imaging.

Government Regulations
National:
There is no NCD on this topic.

Local:
There is an LCD titled "Local Coverage Determination (LCD) for Radiopharmaceutical Agents (L34657)" Revision effective date 1/1/16, Retired 6/1/16

The following radiopharmaceuticals will be considered medically necessary when used with the procedures listed below:

- Iodine I-123 ioflupane, diagnostic, per study dose, up to 5 millicuries (DaTscan™-FDA approved 01/14/2011) (A9584).
- 78607 Brain IMAGING, tomographic (SPECT)

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Deep Brain Stimulation

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/27/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/12	12/13/12	1/3/12	Joint policy established
7/1/13	4/16/13	5/10/13	Policy **position changed** from E/I to **established**; title changed from "Ioflupane I-123 (DaTscan™) Imaging Agent to Detect Parkinson's Disease" to current title; policy extensively rewritten; references updated.
11/01/14	8/21/14	8/25/14	Routine review; policy statement unchanged
7/1/16	4/19/16	4/19/16	Routine maintenance
3/1/17	12/13/16	12/13/16	• Routine maintenance • Continue to diverge from BCBSA (In line with clinical vetting & Hayes) • References in alpha order (not numbered in body of policy)
3/1/18	12/12/17	12/12/17	• Routine maintenance • Updated rationale and references • Added DaT SPECT to distinguish between dementia with Lewy bodies and Alzheimer disease as an inclusion
3/1/19	12/11/19	12/11/19	• Routine maintenance
7/1/19	4/16/19		• Routine maintenance
7/1/20	4/14/20		• Routine maintenance
7/1/21	4/20/21		• Routine maintenance
7/1/22	4/19/22		• Routine maintenance
7/1/23	4/18/23		• Routine maintenance (slp) • Vendor managed: N/A

Next Review Date: 2nd Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: DOPAMINE TRANSPORTER IMAGING WITH SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (DATSCAN™)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, policy guidelines apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.