Dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) is being evaluated to improve the differential diagnosis of degenerative parkinsonian syndromes (PS) from nonparkinsonian tremor and of dementia with Lewy bodies (DLB) from Alzheimer disease (AD).

**Related Policies**
- N/A

**Policy**
Dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) is considered *investigational* for all indications, including but not limited to, aiding in the diagnosis of patients with clinically uncertain parkinsonian syndromes, essential tremor, or dementia with Lewy bodies (DLB), and for the monitoring of disease progression.

**Policy Guidelines**
The SPECT exam would be reported using CPT code 78607 - Brain imaging, tomographic (SPECT).

There is a specific HCPCS code for DaTscan:
- A9584 - Iodine I-123 ioflupane, diagnostic, per study dose, up to 5 millicuries.

**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)) prohibit 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.
**Rationale**

**Background**

Parkinsonian syndromes (PS) are a group of diseases that share similar cardinal signs, characterized by bradykinesia, rigidity, resting tremor and gait disturbance. Parkinson's disease (PD) is the most common cause of parkinsonism; however, diagnosing PD in the early stage of the disease can be difficult. In addition other etiologies such as essential tremor (ET), corticobasal degeneration, multisystem atrophy, progressive supranuclear palsy, vascular parkinsonism, and drug-induced parkinsonism can lead to a similar set of symptoms. Even in specialized movement disorders centers, up to 25% of patients may be misclassified, and some patients, such as those with ET who have been diagnosed with PD, may be erroneously treated. (1) This has led to the development of additional tests to improve the accuracy of clinical diagnosis of PD and other PSs. One recent approach is to evaluate the integrity of dopaminergic pathways in the brain with Dopamine Transporter Imaging with Single Photon Emission Computed Tomography (DAT-SPECT).

DAT-SPECT detects pre-synaptic dopaminergic deficit by measuring dopamine transporter (DAT) binding. In general, striatal DAT binding is reduced in PD, genetic parkinsonism, dementia with Lewy bodies (DLB), corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy, while striatal DAT binding is in the normal range in Alzheimer's disease (AD), ET, dystonic tremor, orthostatic tremor, drug-induced parkinsonism, psychogenic parkinsonism, and vascular parkinsonism. (2) It is proposed that an abnormal DAT-SPECT supports the diagnosis of PD or other neurodegenerative PS (multisystem atrophy, progressive supranuclear palsy), while a normal DAT-SPECT in a symptomatic patient increases the likelihood of a disease not affecting the nigrostriatal dopaminergic pathway.

Due to the degeneration of nigrostriatal neurons in DLB, DAT-SPECT is also proposed to differentiate DLB from AD. Some note a severe sensitivity to neuroleptics (potentially life-threatening) in patients with DLB. However, newer agents are usually well-tolerated, and patients with DLB may also respond to the cholinesterase inhibitors that are more commonly used to treat AD.

Analysis of DAT-SPECT images can be visual or semiquantitative. Since patients typically do not become symptomatic before a substantial number of striatal synapses have degenerated, visual interpretation of the scan is thought to be sufficient for clinical evaluation. A variety of methods are being tested to improve the validity and reliability of ratings, including commercially available software to define the region of interest (ROI) for semiquantitative analysis and the development of an atlas for visual interpretation. Semiquantitative interpretation may aid visual interpretation and, if performed rigorously, may increase diagnostic accuracy; however, interobserver variability tends to be high with manual ROI-based semi-quantification. (3) Semiquantitative analysis also requires normal control values and varies across imaging systems.

Dopamine transporter ligands include $^{123}\text{I}\beta$-CIT, $^{123}\text{I}$-FP-CIT, and $^{99m}$Tc-TRODAT-1. (2) $^{123}\text{I}\beta$-CIT requires a delay between injection and scan of about 24 hours. $^{123}\text{I}$-FP-CIT (DaTscan) is a fluoropropyl derivate of $\beta$-CIT that can be injected 3 to 6 hours before the scan.
Regulatory Status

DaTscan (GE Healthcare) has been in use in Europe since 2000 with a diagnostic indication for use in parkinsonian patients and with expanded use since 2006 in patients suspected of DLB. DaTscan was approved by the U.S. Food and Drug Administration (FDA) in 2011 (National Parkinson Foundation (2011)). The FDA stated that:

DaTscan is indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson’s disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.

Assessment of a diagnostic technology typically focuses on the following three domains:

- Diagnostic Phase I - technical performance (test-retest reliability, agreement among raters)
- Diagnostic Phase II - diagnostic performance (sensitivity, specificity, and positive predictive value [PPV] and negative predictive value [NPV]) in relevant populations of patients, such as those with suspected early Parkinson disease (PD) or inconclusive diagnosis
- Diagnostic Phase III – effect on patient outcomes (demonstration that the diagnostic information can be used to improve patient outcomes through a randomized controlled trial [RCT] or demonstration of a tightly linked chain of evidence from diagnostic accuracy to outcomes)

The criterion standard for the diagnosis of parkinsonian syndromes (PS) and dementia is postmortem neuropathologic examination. In the absence of comparisons with the criterion standard, long-term clinical follow-up may be used as a surrogate standard to evaluate the ability of dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) to discriminate degenerative PS from normality or from non-degenerative disorders that present with similar symptoms, and to discriminate dementia with Lewy bodies (DLB) from Alzheimer disease (AD).

Parkinsonian Syndromes (PS)

Technical Performance

DAT-SPECT is based on the selective affinity of ligands for the dopamine transporter and the exclusive location of the dopamine transporter in dopamine synthesizing neurons. (2) 123I-β-CIT is a cocaine analog that has a high affinity to the dopamine and serotonin transporters. 123I-FP-CIT (DaTscan) is a fluoropropyl derivate of β-CIT that is selective for brain striatal dopamine transporters (DAT), but it can also bind to the serotonin transporter. Although anti-parkinsonian drugs do not interfere with DAT binding, it is unknown if dopamine agonists and levadopa affect DAT expression, which could influence the ability of DAT-SPECT to monitor progression of disease.

A 2011 study evaluated interobserver variability in the visual interpretation of DAT-SPECT. (4) Eighty-nine previously obtained DAT-SPECT scans were blindly reviewed by 3 independent observers with different levels of experience (consultant, resident doctor, radiographer) and classified as either “normal” or “abnormal” and assigned visual DAT-SPECT uptake scores (2-normal, 1-reduced, 0-no uptake). Results were compared with the diagnosis at last visit to
the clinician, divided into PS or no PS. There was good interobserver agreement in 85 of 89 studies for classifying scans as “normal” or “abnormal” (kappa [k] = 0.89-0.93) and moderate agreement in assignment of uptake scores (k = 0.71-0.80 for putamina and 0.50-0.79 for caudate nuclei). All 3 observers achieved a sensitivity of 100%, with specificities of 96, 91, and 89%.

Section Summary

Preclinical studies indicate specificity of ligand binding for the striatal dopamine transporter. There is limited evidence on the effects of medications on dopamine transporter expression. One study reports a high level of interobserver agreement on visual interpretation, suggesting that reliability of visual interpretation is high.

Diagnostic Performance: 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. This study design was used by Marshall et al. (2008) reported a prospective, investigator-initiated industry-funded, 3-year European multicenter study with repeat DAT-SPECT and criterion standard clinical diagnosis (video at 36 months by 2 movement disorders specialists) in 99 diagnostically uncertain cases of PD or essential tremor (ET). (5) Patients with other potential causes of parkinsonism/tremor and patients with major comorbid illness were excluded; 3 healthy volunteers were included. For analysis, the clinical diagnosis was considered as either PD (including atypical PD) or non-PD (including ET, dystonic tremor, vascular parkinsonism). There was 50% loss to follow-up over the 3 years of the study (199 enrolled), although patients with PD were not more likely to drop out than patients without PD. DAT-SPECT scans were evaluated by 3 masked nuclear physicians using visual criteria, and the inter-reader agreement for rating scans as normal or abnormal was high for scans at baseline, 18 months, and 36 months (k = 0.94-0.97).

The 36-month criterion standard diagnosis was degenerative parkinsonism in 71 cases and non-PD in 28 cases. The initial clinical diagnosis had sensitivity of 93% and specificity of 46% compared with diagnosis at follow-up, indicating over-diagnosis of PD. DAT-SPECT at baseline had a sensitivity of 78% and specificity of 97%, with a PPV of 98.2% and NPV of 66.2%. DAT-SPECT scans were considered normal in 21% of the cases with a criterion standard diagnosis of PD and did not change over the 3 years of the study. These cases are referred to as SWEDDS (Subjects with Scans Without Evidence of Dopamine Deficiency) in the literature; it cannot be determined at this time which is more accurate for the diagnosis of these patients, the 36-month clinical assessment or DAT-SPECT. Overall, this is a well-conducted prospective study indicating that an abnormal DAT-SPECT scan may help to confirm a clinical diagnosis of PD. However, the low NPV suggests that a normal DAT-SPECT scan cannot be used to rule out disease. Thus, this test may not be helpful in preventing the potential clinical over-diagnosis of PD.

Brigo et al. (2014) reported a meta-analysis of DAT-SPECT to differentiate between PD and vascular or drug-induced parkinsonism’s. (6) The meta-analysis included 5 studies that had confirmation of the diagnosis after imaging. Both prospective and retrospective studies were included, provided that they included DAT-SPECT as a further diagnostic procedure in patients with an unclear clinical presentation of parkinsonism and had a final diagnosis of PD, vascular parkinsonism, or drug-induced parkinsonism. Pooled sensitivity was 86.2%; specificity was 82.9% for the differential diagnosis between PD and vascular parkinsonism, and 93.8% for the differential diagnosis between PD and drug-induced parkinsonism. There were a number of limitations of the studies, most notably in 3 of the studies it was not clear if the diagnosis at follow-up (criterion standard) was made blinded to the results of DAT-SPECT and could thus be considered an independent
Vlaar et al. (2007) reported a meta-analysis of the diagnostic accuracy of SPECT in the differential diagnosis of PD. They defined studies as clinically relevant when they dealt with the ability of SPECT to identify PD in patients with diagnostic uncertainty, to delineate PD from the other parkinsonian disorders and ET, and to provide an early diagnosis of PD in patients with few signs and symptoms. Studies were included if they had positive tests defined as values of 2 or more SDs below healthy controls or provided raw data that allowed recalculation of the diagnostic accuracy using this cutoff.

Thirty-two trials were included in the analysis in 4 different areas; in more than half of the studies, blinding of the investigator was not described. For diagnosis of PD in an early phase versus normalcy, 6 cross-sectional studies with known PD in an early stage reported sensitivity ranging from 8% to 100% and specificity of 100%. The pooled diagnostic odds ratio (OR) was 60 (95% confidence interval [CI]: 13 to 277). Eight studies were included that evaluated the ability of DAT-SPECT to differentiate between PD and ET and reported sensitivity ranging from 88% to 100% and specificity of 80% to 100% with a pooled diagnostic OR of 210 (95% CI: 79 to 563). Five studies were included that evaluated the diagnostic accuracy of DAT-SPECT to differentiate between PD and vascular parkinsonism; these found sensitivity between 80% to 100% and specificity of 73% to 100% with an OR of 8 (95% CI, 2 to 30). The 11 studies that evaluated the diagnostic accuracy of DAT-SPECT to differentiate between PD and atypical PS had sensitivity from 48% to 100% and specificity from 0% to 33% with a pooled OR of 2 (95% CI: 1 to 4), supporting the view that pre-synaptic ligands cannot distinguish between PD and atypical PS (multisystem atrophy, progressive supranuclear palsy).

The largest study included in the meta-analysis was a 2000 multicenter study by Benamer et al. The study included 158 patients with an established clinical diagnosis of parkinsonism, 27 cases of definite ET, and 35 healthy volunteers. Striatal uptake of the ligand was graded visually as normal or abnormal by an institutional reader who was blinded to the clinical data and a blinded consensus panel of 5 readers. The institutional reader scored 154 of 158 cases of parkinsonism as abnormal, all 27 cases of ET as normal, and 34 of 35 healthy volunteers as normal, resulting in sensitivity of 97% and specificity (for ET) of 100%. For the consensus blinded read, sensitivity and specificity were 95% and 93% respectively. A limitation of this study is the population, which was not comprised of patients with atypical or clinically uncertain parkinsonism or ET.

Vlaar et al. (2008) reported a retrospective study of the diagnostic value of DAT and post-synaptic dopamine receptor binding in 248 patients with unclassified PS. Two investigators established a clinical diagnosis according to generally accepted clinical criteria and were certain enough to make a final diagnosis from the clinical records or after follow-up in all but 25 of the cases. Of the 248 patients, 80 underwent DAT-SPECT alone, 38 underwent dopamine receptor SPECT, and 130 underwent both scans. Scans were analyzed by a nuclear specialist blinded to the clinical diagnosis, with ligand binding of 2 SDs below or above healthy controls considered abnormal. Using clinical diagnosis as the comparator, the OR for DAT-SPECT to distinguish between PD and ET was 82, between PD and vascular parkinsonism, was 61, between PD and drug-induced parkinsonism, was 36, and between PD and atypical PS, was 1. Because there was uncertain clinical diagnosis in only 25 patients, this does not appear to be an appropriate patient population, the semiquantitative image analysis may not be representative, and the study was retrospective.
Section Summary

The literature on diagnostic performance includes meta-analyses of a number of small studies along with a large and well-conducted industry-sponsored study on the diagnostic accuracy of DAT-SPECT. In general, this evidence supports moderately high sensitivity and high specificity for the test. However, most of these studies have methodologic limitations, primarily the lack of a true criterion standard for the diagnosis of PSs. In the highest quality study, in which the criterion standard was 36-month clinical diagnosis by a panel of independent experts, the sensitivity and specificity of testing was 78% and 97%, respectively. The PPV was 98.2% and the NPV was 66.2% in a population of patients with a prevalence of underlying PD of approximately 70%. This indicates that in a population of patients with a high pretest likelihood of PD, a positive test may be useful in confirming PD, while a negative test is less useful in ruling out the disorder.

Clinical Utility: The most rigorous evaluation of the impact of a diagnostic test on clinical outcomes is a RCT that evaluates health outcomes in patients who received the new diagnostic test compared with patients who are evaluated without the new test according to the standard of care. Kupsch et al. (2012) reported an industry-sponsored open-label multicenter randomized trial from 19 university hospital centers in Europe and the U.S. that assessed the impact of DAT-SPECT on diagnosis, confidence of diagnosis, clinical management, health resource use, and safety in 273 patients with clinically uncertain PSs. Criteria of uncertainty included at least 1 of the following: only 1 of the 3 cardinal signs of parkinsonism; 2 signs without bradykinesia; atypical signs; signs of mild intensity; poor response to L-dopa and lack of disease progression. After the baseline visit and establishment of a clinical management plan, patients were randomized to DAT-SPECT or no-imaging controls; the DAT-SPECT scans were visually classified as normal or abnormal by a nuclear medicine physician at each center who was blinded to clinical signs and/or symptoms. Patients were then followed for 1 year (visits at 4 weeks, 12 weeks, 1 year) by neurologists with (n=12) or without (n=7) movement disorder specialization.

The primary outcome was the proportion of patients in the efficacy population (baseline and 12-week visits) who had 1 or more changes in clinical management. Significantly more patients in the DAT-SPECT group had at least 1 change in their clinical management plan by 12 weeks compared with the control group (50% vs. 31%, p=0.002). This was due to a greater change in management by movement disorder specialists (51% DAT-SPECT vs. 28% controls, p<0.001). Medications were initiated in 29% of patients and withdrawn in 18% of patients after DAT-SPECT (patients could be counted in both categories). Changes included initiation of dopaminergic therapy or more aggressive dopaminergic therapy in patients with an abnormal scan, discontinuation of dopaminergic therapy, or initiation of tremor control drugs in patients with a normal scan, and unplanned diagnostic tests. For the general neurologists, clinical management was not affected by the DAT-SPECT results, with a change in management in 48% of DAT-SPECT patients versus 43% of controls (p=NS). Changes in diagnosis occurred in 45%, 46%, and 54% of DAT-SPECT patients by 4 weeks, 12 weeks, and 1 year, respectively, (per protocol population) compared with a change in diagnosis in 9%, 12%, and 23% of control patients at the same time points (p<0.001 for all comparisons). The changes were in the direction of better agreement between the clinical diagnosis and imaging results. Clinicians had increased confidence in diagnosis at 4 weeks, 12 weeks, and 1 year in the DAT-SPECT group; the greatest change in confidence in diagnosis was for patients with an initial inconclusive diagnosis (62% vs. 22% controls, p<0.001). There were no significant differences in quality of life or health resource utilization during the 1-year follow-up period. No serious adverse events
Catafau and Tolosa (2004) reported a prospective multi-center trial of the impact of DAT-SPECT on diagnosis and clinical management of 118 patients with clinically uncertain PS, with 2-year follow-up reported in 2007. Criteria of uncertainty were assessed by referring neurologists and included at least 1 of the following: only 1 of the 3 cardinal signs of parkinsonism, with or without asymmetry; 2 signs without bradykinesia; atypical signs; signs of mild intensity; poor response to L-dopa, and lack of disease progression. Excluded were patients with an established clinical diagnosis and patients where the uncertainty was between PD, multisystem atrophy, and progressive supranuclear palsy. Following clinical diagnosis into categories (pre-synaptic or non-pre-synaptic PS, or inconclusive diagnosis), all patients underwent DAT-SPECT with visual assessment of images by trained nuclear medicine physicians. After reviewing the DAT-SPECT results, the neurologists again provided a diagnosis and recorded proposed changes in the planned management. At baseline, 67 patients were classified as suspected pre-synaptic PS, 26 as suspected non-pre-synaptic PS, and 25 as inconclusive. DAT-SPECT results were not consistent with the initial diagnosis in 36% of patients with suspected pre-synaptic PS (normal image) and 54% of patients with non-pre-synaptic PS (abnormal image). After imaging, 76% of inconclusive patients were reclassified and 16 patients (14%) were reclassified as inconclusive. Overall, imaging resulted in a change in the diagnosis in 52% of patients and to a change in management in 72% of cases. All patients with a final diagnosis of pre-synaptic PS had an abnormal image, whereas 94% of patients with non-pre-synaptic PS had a normal scan.

At 2 years, 85 patients (72%) were available for follow-up. In 8 patients (9.4%) the neurologist was unable to provide a definite diagnosis, and in 69 of the remaining 77 patients (90%), the initial DAT-SPECT results agreed with the clinical diagnosis at follow-up. The rate of agreement was higher when the final diagnosis was pre-synaptic PS (97%) than when it was non-pre-synaptic PS (77%). The rate of agreement between clinical diagnosis at baseline (before DAT-SPECT) and follow-up was 56%. This increased to 81% when the diagnosis after DAT-SPECT was compared with the diagnosis at follow-up. If clinical diagnosis at follow-up differed from that suggested by the initial scan (6 of 8 agreed to a second scan) or was inconclusive (n=8), a second DAT-SPECT scan was performed. There were discrepancies between the first and second scans in 6 of the 14 patients, and in 5 of these 6, the initial scan was considered abnormal. The second DAT-SPECT results helped to establish a diagnosis in 7 of 8 patients (87.5%) with a previously inconclusive diagnosis.

Bairactaris et al. (2009) evaluated the impact of DAT-SPECT on diagnoses of patients with PS. Sixty-one consecutive patients with an initial diagnosis of parkinsonism (n=40) or uncertain tremor disorder (n=21) by their treating community neurologist were re-examined by 2 neurologists who were blinded to the original diagnosis (overall agreement between the 2 of 75.7%, k=0.461). Patients then underwent DAT-SPECT imaging, which was evaluated by 2 masked independent and experienced nuclear medicine physicians using a semiquantitative approach and classified as normal or abnormal (k=0.855). Based on DAT-SPECT imaging, the initial diagnosis was altered for 21 patients (34.4%) relative to the initial classification from the community neurologist and for 6 patients (9.8%) diagnosed at their center. All patients were re-examined by 2 neurologists at the center after 1 year of follow-up and classified as having neurodegenerative or non-neurodegenerative disorders. With the final diagnosis as the reference standard, DAT-SPECT had a sensitivity of 95%, specificity of 82% and PPVs and NPVs of 90%. Although this study appears to have been well-conducted,
evaluation of DAT-SPECT scans by 2 experienced nuclear medicine physicians using a semi-quantitative approach may not be representative of results obtained outside of the investigational setting. As noted by the authors, DAT-SPECT studies did not appear to add a great deal to the diagnosis made by an expert in movement disorders.

Sixel-Doring et al. (2011) reported a retrospective study of the role of DAT-SPECT in the differential diagnosis of 125 consecutive patients with diagnostically uncertain parkinsonian or non-parkinsonian tremor syndromes.(15) All patients presented with an unclear diagnosis of tremor and/or parkinsonian symptoms and/or poor treatment response, and all scans were assessed both visually and semi-quantitatively with a standard region of interest (ROI) template and compared with healthy controls. If the suspected clinical diagnosis was not confirmed by DAT-SPECT, cases were reassessed in a clinical follow-up after 3 to 6 months. A total of 36/40 patients (90%) with the predominant clinical feature of a postural and/or kinetic tremor (non-parkinsonian tremor) showed normal DAT-SPECT while 73/85 (86%) with predominant clinical symptoms of PD showed abnormal DAT-SPECT. Clinical reassessment of the 12 clinically suspected PD patients who had normal DAT-SPECT (14%) led to a revised diagnosis in 7 cases (2 patients with dystonic tremor, 4 cases of non-neurologic disease, and 1 showed a complete and spontaneous remission of symptoms). For 5 patients with a positive response to levodopa, and for 4 cases that were diagnosed with non-parkinsonian tremor but had abnormal DAT-SPECT and were not responsive to levodopa, the diagnosis remained unclear. Overall, DAT-SPECT led to a revised diagnosis in 5.6% of cases and inconclusive diagnosis in 7.2% in this retrospective analysis from a specialized movement disorders center.

Other literature indicates that the level of DAT-SPECT binding does not predict disease severity or have prognostic value for the progression of motor symptoms in PD. (16, 17)

Section Summary

Evidence on clinical utility includes a well-conducted RCT, a prospective multicenter trial, and several retrospective studies that have evaluated the effect of DAT-SPECT on diagnosis and changes in treatment. These studies report that the use of this test can result in changes in diagnosis in a minority of patients, greater confidence in the diagnosis by the treating clinician, and changes in treatment such as medication management. However, there is no direct evidence that these changes result in improvements in health outcomes. A limitation of this evidence is the lack of a criterion standard diagnosis to evaluate if the changes were in the direction of more accurate diagnosis and more appropriate management. For example, the RCT showed that more patients evaluated with DAT-SPECT have changes in diagnosis and management compared with controls without imaging; however, no improvement in quality of life was observed within the 1-year follow-up. Therefore, clinical utility has not been established, because the evidence is not sufficient to conclude that health outcomes are improved as a result of testing.

Dementia with Lewy Bodies

Technical Performance: As above

Diagnostic Performance: The largest study to evaluate DAT-SPECT for DLB is a prospective, investigator initiated, industry-sponsored, multicenter study by McKeith et al. (2007) who assessed 326 patients with clinical diagnosis of probable (n=94) or possible (n=57) DLB or non-DLB (n=147).(18) In 28 patients, no diagnosis was made. The diagnoses were established by a consensus panel of 3 clinicians who did not have access to DAT-SPECT results, and DAT-SPECT scans were assessed visually by 3 nuclear physicians with expertise in DAT-SPECT imaging who were unaware of the clinical
diagnosis. DAT-SPECT had a mean sensitivity of 77.7% for detecting a clinical probable DLB, a specificity of 90.4% for excluding non-DLB dementia, PPV of 82.4% and NPV of 87.5%. This study did not use long-term clinical follow-up as the standard.

Papathanasiou et al. (2012) reported a meta-analysis of the diagnostic accuracy of DAT-SPECT in DLB. Four studies with a total of 419 patients were included in the meta-analysis, including the study by McKeith et al. (2007) previously described. The studies included both patients with an uncertain diagnosis and patients with an already certain diagnosis. Three of the studies used clinical diagnosis as the reference standard while one used post-mortem histopathology. The estimated pooled sensitivity of DAT-SPECT to differentiate DLB from no DLB was 86.5%, the specificity was 93.6%, and the diagnostic OR was 48.95. Funnel plot analysis showed no significant publication bias. These results might be altered if the reference standard (clinical diagnosis) is flawed. The sole study to assess diagnostic accuracy in histologically verified cases (n=23) reported no false negatives and sensitivity of 100%.

Siepel et al. (2013) reported a longitudinal study of patients who had inconsistent findings between clinical criteria for DLB and DAT-SPECT results at baseline. Fifty patients were evaluated with clinical criteria and DAT-SPECT results and followed for 2 to 5 years. Twenty-eight patients met clinical criteria for DLB or non-DLB; the remaining patients were clinically inconclusive and were not included in the analysis. For 18 patients the DAT-SPECT scan and clinical criteria were concordant. Blinded analysis showed 7 patients who had an abnormal scan but did not initially meet the clinical criteria for DLB developed typical clinical features over follow-up. Three patients who met clinical criteria for DLB but had a normal DAT-SPECT at baseline continued to meet clinical criteria for DLB over follow-up, indicating a false negative scan (SWEDD) in 6% of patients. The study is limited by the small number of subjects and the lack of autopsy findings to confirm the diagnosis.

Clinical Utility: Kemp et al. (2011) conducted a retrospective study of the impact of DAT-SPECT on the clinical diagnosis and subsequent management of 80 consecutive patients with possible DLB. The patients had been referred for imaging with suspected DLB by 33 specialists in older-age psychiatry working at 11 memory clinics in the U.K. All DAT-SPECT scans were interpreted visually by a single observer in conjunction with the clinical referral details and any other relevant imaging. DAT-SPECT imaging results were found to be abnormal (indicating DLB) in 20 (25%) and normal in 60 (75%) patients. Of the 20 patients with an abnormal scan, 18 had a post-scan working clinical diagnosis of DLB (90%), 1 had a diagnosis of vascular dementia (5%), and 1 had no recorded outcome (5%). Fifty-eight of the 60 patients with a normal DAT-SPECT scan had an alternative clinical diagnosis (95%). Subsequent to DAT-SPECT, scan findings and diagnoses were discussed with patients and/or their caregivers in 94% of cases.

Pharmacologic management affecting anti-psychotic, dopaminergic or cholinergic medication was changed in about half of the patients after the scan, although many of the patients (irrespective of the imaging results) were in the earliest phase of their disease process and did not require immediate treatment for their symptoms. In addition, the small numbers did not allow substantive conclusions about changes in specific therapies.

Summary

Dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) is being evaluated to improve the differential diagnostic of parkinsonian syndromes (PS) from non-parkinsonian tremor and of dementia with Lewy bodies (DLB)
from Alzheimer’s disease (AD). Most of the available literature is from Europe, where a ligand has been available for over a decade. In terms of technical performance, the ligand is specific for the striatal dopamine transporter, and studies indicate reliability in assessment of the images when performed by experienced readers.

For diagnosing Parkinson disease (PD) in patients with parkinsonian symptoms, studies of diagnostic accuracy report good specificity for confirming nigrostriatal degeneration, with less sensitivity for ruling out disease. These findings are dependent, however, on a reference standard (clinical diagnosis) which may be flawed, and it is unknown whether DAT-SPECT would show greater sensitivity when compared with the criterion standard of histopathologic diagnosis. Evidence on clinical utility includes a randomized controlled trial that showed more patients evaluated with DAT-SPECT have changes in diagnosis and management compared with controls without imaging; however, no improvement in quality of life was observed within the 1-year follow-up. In other studies, DAT-SPECT findings are consistent with about 90% of diagnoses made by specialists in movement disorders and that in a relatively small proportion of patients, the diagnosis has been altered based on DAT-SPECT.

For discriminating between DLB and AD, the sensitivity and specificity of DAT-SPECT is somewhat lower than for PS, although the comparison standard used in the available studies may be flawed. One retrospective community-based study suggests that DAT-SPECT may influence the clinical diagnosis and management of a large proportion of patients with possible DLB.

Overall, the evidence available at this time is insufficient to determine with certainty the effect of this technology on health outcomes. Therefore, DAT-SPECT is considered investigational.

**Practice Guidelines and Position Statements**

The American College of Radiology (ACR) published appropriateness criteria for dementia and movement disorders in 2010.(22) ACR did not give an appropriateness rating for functional imaging of the dopamine transporter (DAT) using SPECT. However, the summary of literature review states that functional imaging of the dopamine transporter using SPECT can help to distinguish DLB from AD.

The 2006 practice parameters (reaffirmed in July 2013) from the American Academy of Neurology state that $\beta$-CIT and IBZM SPECT are possibly useful in distinguishing PD from essential tremor (5 Class III studies).(23) There was insufficient evidence to determine if these modalities are useful in distinguishing PD from other forms of parkinsonism.

The International Society of Nuclear Medicine, now called the Society of Nuclear Medicine and Molecular Imaging, provided a practice guideline for dopamine transporter imaging with SPECT in 2011.(3) The guideline states that the main indication for DAT-SPECT is striatal DAT visualization in the evaluation of adult patients with suspected PS to help differentiate ET from tremor due to pre-synaptic PS (PD, multiple-system atrophy, progressive supranuclear palsy). Other indications are the early diagnosis of pre-synaptic PS, differentiation of pre-synaptic PS from parkinsonism without pre-synaptic dopaminergic loss, such as drug-induced parkinsonism or psychogenic parkinsonism, and differentiation of DLB from AD. The guidance states 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.
The European Federation of Neurological Societies and Movement Disorder Society-European Section (EFNS/MDS-ES) published recommendations for the diagnosis of PD in 2013. (24) EFNS/MDS-ES provided a Level A recommendation for the use of DAT-SPECT in the differential diagnosis between degenerative parkinsonism and ET. The guidelines specify that DAT-SPECT is indicated in the presence of significant diagnostic uncertainty and particularly in patients presenting atypical tremor manifestations.

The European Association of Nuclear Medicine Neuroimaging Committee published updated guidelines on procedures for DAT-SPECT in 2010, based on the individual experience of experts in European countries.(25) The guidelines state that 123I-FP-CIT imaging is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain PD and for the differentiation of dementia with Lewy bodies 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 (e.g., neuroleptic-induced parkinsonism). The guidelines state 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 ROI.

The U.K.’s National Institute for Health and Clinical Evidence (NICE) published a clinical guideline on the diagnosis and management of PD in 2006.(26) The guideline states that 123I-FP-CIT SPECT 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) and that 123I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation (based on level of evidence IV, expert opinion).

NICE published a clinical guideline on dementia in 2006.(27) The guideline recommends that dopaminergic iodine-123-radiolabeled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT should be used to help establish the diagnosis in those with suspected DLB if the diagnosis is in doubt.

U.S. Preventative Services Task Force Recommendations

Dopamine transporter imaging is not a preventive service.

Medicare National Coverage

None identified.

References

4. Papathanasiou N, Rondogianni P, Chroni P et al. Interobserver variability, and
Medical Policy


19. Papathanasiou ND, Boutsidis A, Dickson J et al. Diagnostic accuracy of (1)(2)(3)I-FP-CIT (DaTSCAN) in dementia with Lewy bodies: a meta-analysis of

**Documentation Required for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services are considered investigational and therefore not covered for any indication.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>78607</td>
<td>Brain imaging, tomographic (SPECT)</td>
</tr>
</tbody>
</table>
HCPC | A9584 | Iodine 1-123 ioflupane, diagnostic, per study dose, up to 5 millicuries
ICD-9 Procedure | None |
ICD-10 Procedure | For dates of service on or after 10/01/2015 |
ICD-9 Diagnosis | All Diagnoses |
ICD-10 Diagnosis | For dates of service on or after 10/01/2015 |
All Diagnoses |

Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/28/2013</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>9/30/2014</td>
<td>Policy title change from Dopamine Transporter Imaging with Single Photon Emission Computed Tomography (DAT-SPECT)</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td></td>
<td>Policy revision without position change</td>
<td></td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

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**

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

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 also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.