Dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) is investigational for all indications, including but not limited to:

- Aiding in the diagnosis of patients with clinically uncertain parkinsonian syndromes; OR
- Distinguishing between parkinsonian syndromes and essential tremor; OR
- Distinguishing between dementia with Lewy bodies and Alzheimer disease; OR
- Monitoring of disease progression

Related Policies

7.01.63 Deep Brain Stimulation

Policy Guidelines

Coding

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>78607</td>
<td>Brain imaging, tomographic (SPECT)</td>
</tr>
</tbody>
</table>

HCPCS

| A9584        | Iodine I-123 ioflupane, diagnostic, per study dose, up to 5 millicuries |

Description

Dopamine transporter imaging with single -photon emission computed tomography (DAT-SPECT) is being evaluated to improve the differential diagnosis of parkinsonian syndromes from nonparkinsonian tremor and of
Background
Parkinsonian syndromes (PS) 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; 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. 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 using dopamine transporter single-photon emission computed tomography (DAT-SPECT).

DAT-SPECT detects presynaptic dopaminergic deficit by measuring 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 AD, ET, dystonic tremor, orthostatic tremor, drug-induced parkinsonism, psychogenic parkinsonism, and vascular parkinsonism. 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, semi-quantitative, or quantitative. Because patients typically do not become symptomatic before a substantial number of striatal synapses have degenerated, visual interpretation of the scan is thought to be sufficient for clinical evaluation. A variety of methods are being tested to improve the validity and reliability of ratings, including commercially available software to define the region of interest (ROI) for analysis and the development of an atlas for visual interpretation. Quantitative interpretation may aid visual interpretation and, if performed rigorously, may increase diagnostic accuracy; however, interobserver variability tends to be high with manual ROI-based semiquantification. Semiquantitative analysis also requires normal control values and varies across imaging systems.

Dopamine transporter ligands include 123I-β-CIT, 123I-FP-CIT, and 99mTc-TRODAT-1. 123I-β-CIT requires a delay between injection and scan of about 24 hours. 123I-FP-CIT (DaTscan™) is a fluoropropyl derivate of β-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 Drug Administration (FDA) in 2011 and 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.” FDA product code: KPS.

Scope
Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject
to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

**Benefit Application**

N/A

**Rationale**

This evidence review was created in August 2012 and updated periodically with a search of the MEDLINE database. The most recent literature review was performed through June 4, 2015.

Assessment of a diagnostic technology typically focuses on the following 3 categories of evidence: 1) Technical Performance (test-retest reliability, agreement among raters); 2) Diagnostic accuracy (sensitivity, specificity, 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; and 3) 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 (DAT) 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).

**Technical Performance**

DAT-SPECT is based on the selective affinity of ligands for the DAT and the exclusive location of the DAT in dopamine synthesizing neurons. (2) $^{123}$I-β-CIT is a cocaine analog that has a high affinity to the DAT and serotonin transporters. $^{123}$I-FP-CIT (DaTscan™) is a fluoropropyl derivate of β-CIT that is selective for brain striatal 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 levodopa affect DAT expression, which could influence the ability of DAT-SPECT to monitor progression of disease.

A 2012 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), classified as “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” (κ range, 0.89-0.93) and moderate agreement in assignment of uptake scores (κ range, 0.71-0.80 for putamina; 0.50-0.79 for caudate nuclei). All 3 observers achieved a sensitivity of 100%, with specificities of 96%, 91%, and 89%.

In 2014, Seibyl et al. reported intra- and interrater agreement for DAT-SPECT images with data from 5 multicenter trials (818 patients). (5) DAT binding was classified as “normal” or “abnormal.” Within-reader agreement was assessed in 1 study, and showed complete (100%) agreement when image evaluation was blinded. In all trials, between-reader agreement was high (κ>0.8) for PD, but decreased when comparing blinded image evaluation and on-site readers for DLB. Sensitivity and specificity values obtained from individual studies are described in more detail next.
Section Summary: DAT-SPECT Technical Performance

Preclinical studies indicate specificity of ligand binding for the striatal DAT. There is limited evidence on the effects of medications on DAT expression. Studies report a high level of interobserver agreement on visual interpretation of images for PD, suggesting that reliability of visual interpretation for this disorder is high. There was less interobserver agreement on visual interpretation of images for DLB.

Parkinsonian Syndromes

Diagnostic Accuracy

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., who in 2009 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).(6) 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 (κ range, 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 overdiagnosis of PD. DAT-SPECT at baseline had a sensitivity of 78% and specificity of 97%, with a PPV of 98.2% and an 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); 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 was 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 overdiagnosis of PD.

In 2015, Jakobson et al. reported a prospective study on the diagnostic accuracy of visual assessment of DAT-SPECT in individuals with early-stage parkinsonian diseases. (7) Strengths of this study include an independent clinical diagnosis made at baseline and follow-up, and blinded reading of the DAT scans. Patients (N=171) were identified incidentally from an ongoing longitudinal population-based research project on parkinsonian disorders. All met criteria for stage 1 disease on the U.K. Parkinson’s Disease Society Brain Bank clinical criteria for PD. Patients with a Mini-Mental State Examination scores less than 24 or evidence of ET or secondary parkinsonism were excluded. The results of DAT-SPECT were compared with criterion-based clinical diagnoses at a mean follow-up of 4.6 years. The clinical diagnoses at baseline and follow-up were performed independently of DAT-SPECT findings. Image analysis was performed by 2 nuclear medicine specialists who were blinded to the clinical diagnosis. The study also included 37 age-matched healthy controls who underwent DAT-SPECT imaging for evaluation of specificity. There was a discrepancy between the reviewers in 10 cases (9.3%); these were reevaluated to reach a consensus. Visual assessment in this enriched population was found to have a sensitivity of 94% and specificity of 92%, with 3 of 37 controls considered false positives and 10 of 171 patients considered false negatives at baseline. However, at this time, it is not known if the SWEDDS are true false negatives or were misdiagnosed as having a PS.

A number of published studies and meta-analyses have not included an independent reference standard of either blinded clinical diagnosis at follow-up or post mortem analysis of substantia nigra neuron degeneration. 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 with caution.

For example, in 2014 Brigo et al. reported a meta-analysis of DAT-SPECT to differentiate between PD and vascular or drug-induced parkinsonisms. (8) The meta-analysis included 5 studies that had diagnosis confirmed
by imaging. There were a number of study limitations, most notably, in 3 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 reference standard. Two studies published in 2014 analyzed data from Kupsch et al. (see next). (9) The studies included 92 patients with clinically uncertain parkinsonian syndromes (CUPS) at baseline who had confirmed clinical diagnosis at 1 year. Bajaj et al assessed the effect of age, disease stage, and other clinical and neurocognitive measures on the diagnostic performance of DAT-SPECT.10 Hauser et al reported that the diagnostic accuracy of DAT-SPECT was higher than clinical diagnosis at baseline.11 Both studies are limited because clinical diagnosis at 1 year was influenced by the imaging results and cannot be considered an independent reference standard.

Other studies provide limited information on diagnostic accuracy because they were not conducted in an appropriate population that included patients with clinically uncertain PD or ET. For example, a 2000 multicenter study by Benamer et al. included 158 patients with an established clinical diagnosis of parkinsonism, 27 cases of definite ET, and 35 healthy volunteers. (12) 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.

In 2014, O'Brien et al. published an industry-funded pooled analysis of 4 clinical studies that were submitted in support of the new drug application to the U.S. Food and Drug Administration (FDA). (13) All studies assessed the sensitivity and specificity of DAT-SPECT to detect nigrostriatal cell loss in patients with signs and symptoms of movement disorders and/or dementia. The clinical diagnosis, determined at baseline or at 12, 24, or 36 months after imaging, was performed independently of DAT-SPECT results in 3 of the 4 studies. The study populations ranged from patients with uncertain clinical diagnosis to patients with established clinical diagnosis. Pooled analysis showed sensitivity of 93.1% (range, 75.0%-96.5%) and specificity of 91.1% (range, 83%-100%) in the intention-to-treat population of 726 patients. Interpretation of this study is limited by heterogeneity in the included studies. Only 2 studies included a population of patients with an uncertain diagnosis, one of which was an open-label phase 4 study where the clinical diagnosis was not independent of DAT-SPECT. Individual studies are described in greater detail in the Clinical Utility section.

Vlaar et al. reported a retrospective study of the diagnostic value of DAT and post-synaptic dopamine receptor binding in 248 patients with unclassified PS in 2008. (14) 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 medicine specialist blinded to the clinical diagnosis, with ligand binding of 2 SDs above or below healthy controls considered abnormal. Using clinical diagnosis as the comparator, the odds ratio [OR] for DAT-SPECT to distinguish between PD and ET was 82; between PD and vascular parkinsonism, it was 61; between PD and drug-induced parkinsonism, it was 36; and between PD and atypical PS, it was 1. Because there was uncertain clinical diagnosis in only 25 patients, this does not appear to be an appropriate patient population, the semi-quantitative image analysis may not be representative, and the study was retrospective.

Diagnostic accuracy of DAT-SPECT can be compared with the diagnostic accuracy of clinical diagnosis. A longitudinal study by Adler et al. found that, compared with neuropathologic findings of PD as the criterion standard, clinical diagnosis by a movement disorder specialist of possible PD (n=34) had only 26% accuracy. (15) Clinical diagnosis by a movement disorder specialist of probable PD (n=97) on the first visit had 53% PPV in cases with a disease duration less than 5 years and 88% PPV in patients with disease duration of 5 years or more. Jouhta et al. reported a retrospective study of the diagnostic accuracy of PD by general neurologists. (16) Of 1362 individuals who had been examined post mortem, 122 cases were identified with a clinical and/or neuropathologic diagnosis of PD. The sensitivity of clinical diagnosis of PD was 89.2% and the specificity was 57.8% compared with post mortem neuropathologic diagnosis, indicating that 1 in 4 diagnoses by general neurologists was incorrect.

Section Summary: Diagnostic Accuracy of DAT-SPECT in Patients With PS
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 studies had methodologic limitations, primarily the lack of a true criterion standard for the diagnosis of PS. 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 pre-test likelihood of PD, a positive test may be useful in confirming PD, while a negative test is less useful in ruling out the disorder.

**Effect on Health Outcomes**

The most rigorous evaluation of the impact of a diagnostic test on clinical outcomes is an 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. In 2012-2013, Kupsch et al. reported an industry-sponsored, open-label, multicenter randomized trial from 19 university hospital centers in Europe and the United State that assessed the impact of DAT-SPECT on diagnosis, confidence of diagnosis, clinical management, health resource use, and safety in 273 patients with CUPS. (9,17) Criteria of uncertainty included at least one of the following: only one 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 one or more changes in clinical management. Significantly more patients in the DAT-SPECT group had at least one change in their clinical management plan by 12 weeks than 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 occurred during the study.

In 2004, Catafau and Tolosa reported a prospective multicenter trial of the impact of DAT-SPECT on diagnosis and clinical management of 118 patients with CUPS, with 2-year follow-up reported in 2007. (18,19) Criteria of uncertainty were assessed by referring neurologists and included at least one 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 (presynaptic or nonpresynaptic PS, or inconclusive diagnosis), all patients underwent DAT-SPECT with visual assessment of images by a trained nuclear medicine physician. 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 presynaptic PS, 26 as suspected nonpresynaptic PS, and 25 as inconclusive. DAT-SPECT results were not consistent with the initial diagnosis in 36% of patients with suspected presynaptic PS (normal image) and 54% of patients with nonpresynaptic PS (abnormal image). After imaging, 19 (76%) inconclusive patients were reclassified and 16 of 118 patients (14%) were reclassified as inconclusive. Overall, imaging resulted in a change in the diagnosis in 52% of patients and in a change in management in 72% of cases. All patients with a final diagnosis of presynaptic PS had an abnormal image, whereas 94% of patients with nonpresynaptic PS had a
normal scan.

At 2 years, 85 patients (72%) were available for follow-up. (19) 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 presynaptic PS (97%) than when it was non-presynaptic 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 (6/8 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. evaluated the impact of DAT-SPECT on diagnoses of patients with PS in a 2009 report. (20) 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, 75.7%; $\kappa$=0.461). Patients then underwent DAT-SPECT imaging, which was evaluated by 2 masked independent and experienced nuclear medicine physicians using a semi-quantitative approach and classified as normal or abnormal ($\kappa$=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 at 1-year 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.

Additional retrospective studies support a change in diagnosis and increase in confidence in diagnosis following DAT-SPECT. Several tertiary referral centers have reported a change in diagnosis and management for a majority of patients with CUPS. (21-23) Sadasivan and Friedman also reported on the clinical outcome of the change in management. (23) Sixty-five CUPS patients were referred for DAT-SPECT over a 17-month period. Scans were abnormal in 22 patients, leading to a final diagnosis of PD in 22 patients and a change in management in 41 patients (63%). Of the 41 patients with a change in management, 30 (73%) were clinically stable or improved at follow-up. This included 10 patients who were found to have drug-induced PD without any striatal neurodegeneration, leading to discontinuation or reduction in dose of the drug.

Another study from a tertiary care center evaluated 83 scans ordered over a 2-year period with specific features that led the physician to question the diagnosis. (22) The greatest impact was to differentiate ET from PD, with a change in diagnosis, management, or both in 72.2% of these patients. In a retrospective review of the effect of DAT-SPECT on diagnosis by referring physicians, Siebert and Weiner found that confidence in a diagnosis of PD or non-PD was significantly increased with abnormal scans, but not with normal scans. (24) For many patients, the scan confirmed the diagnosis of PD, despite a poor response to medication and resulted in a change in medication.

A retrospective study from a hospital imaging facility in Europe evaluated whether routine clinical requests for DAT-SPECT were considered appropriate or inappropriate and whether the results led to a change in management. (25) Appropriateness was determined by consensus of 2 movement disorders specialists, and a request was considered inappropriate if DAT-SPECT was unable to answer the question or if DAT-SPECT results would not change patient care. For example, a differential diagnosis between parkinsonian tremor and ET was considered appropriate, while evaluation of the severity of dopaminergic cell loss in already diagnosed PD was always considered to be inappropriate. Of 516 consecutive requests over an 8-year period, 37% were considered inappropriate. They included requests to assess the degree of dopaminergic denervation in already diagnosed patients (n=40) and confirmation of a clinically evident diagnosis (n=64). Scan requests by movement disorder specialists were considered appropriate more frequently than requests from other physicians (79% vs. 57%, p<0.01). A change in management was identified in 13% of patients with an inappropriate scan compared with 92% of the patients with an appropriate scan, and a change in management was more frequently observed if the scan was requested by movement disorders specialists than by other physicians (71% vs. 56%, p=0.01).

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. (26,27)

Section Summary: Effect on Health Outcomes of DAT-SPECT in Patients With Clinically Uncertain PD

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 technology can result in changes in diagnosis in a minority of patients, greater confidence in the diagnosis by the treating clinician, and changes in treatment (e.g., medication management). However, there is only 1 retrospective series to indicate that these changes result in improvements in health outcomes. A limitation of this evidence is the lack of a criterion standard diagnosis to evaluate whether 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 than controls without this technology; however, no improvement in quality of life was observed by the 1-year follow-up.

Dementia with Lewy Bodies

Diagnostic Accuracy

The largest study to evaluate DAT-SPECT for DLB is a 2007 prospective, investigator initiated, industry-sponsored, multicenter study by McKeith et al., who assessed 326 patients with clinical diagnosis of probable (n=94) or possible (n=57) DLB or non-DLB (n=147). (28) 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 medicine physicians with expertise in DAT-SPECT imaging who were unaware of the clinical diagnosis. DAT-SPECT had a mean sensitivity of 77.7% for detecting clinical probable DLB, a specificity of 90.4% for excluding non-DLB dementia, a PPV of 82.4%, and an NPV of 87.5%. This study did not use long-term clinical follow-up as the standard.

Papathanasiou et al. reported a meta-analysis of the diagnostic accuracy of DAT-SPECT in DLB in 2012. (29) Four studies with a total of 419 patients were included in the meta-analysis (including the study by McKeith et al previously described). The studies included both patients with an uncertain diagnosis and patients with a certain diagnosis. Three 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 non 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 differ 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%.

In 2013, Siepel et al. reported a longitudinal study of patients who had inconsistent clinical criteria for DLB and DAT-SPECT results at baseline. (30) Fifty patients were evaluated with clinical criteria and DAT-SPECT results and followed for 2 to 5 years. Twenty-eight patients met clinical criteria for DLB or non-DLB; the remaining patients were clinically inconclusive and not included in the analysis. For 18 patients the DAT-SPECT scan and clinical criteria were concordant. Blinded analysis showed 7 patients who had an abnormal scan but did not initially meet the clinical criteria for DLB developed typical clinical features over follow-up. Three patients who met clinical criteria for DLB but had a normal DAT-SPECT at baseline continued to meet clinical criteria for DLB over follow-up, indicating a false-negative scan (SWEDD) in 6% of patients. The study is limited by the small number of subjects and the lack of autopsy findings to confirm the diagnosis.

Effect on Health Outcomes

In 2015, Walker et al. reported an industry-funded RCT to determine whether DAT-SPECT would lead to a change in diagnosis and more confidence in diagnosis in patients with probable DLB or non-DLB dementia. (31) Patients were included in the study if they were diagnosed as possible DLB by local physicians (neurologists or geriatric psychiatrists). Patients were included if they had dementia and either 1 core feature or 1 or more suggestive features of DLB. Excluded from the study were patients with an established clinical diagnosis of probable DLB or non-DLB dementia; Parkinson features for more than 1 year; significant vascular pathology; severe mental or physical illness that could account for dementia; or a medication known to influence DAT-SPECT binding (including amphetamine, benatropine, bupropion, cocaine, mazindol, methylphenidate, phentermine, and sertraline). A total of 187 patients were randomized in a 2:1 ratio to have DAT-SPECT scans or clinical diagnosis alone. Onsite clinicians recorded DLB features and rated their confidence in diagnosis using a
visual analog scale (VAS, 0-100). The readers, who had variable expertise, rated 57% of scans as normal and 43% as abnormal. At both 8- and 24-week follow-ups, the onsite clinicians were more likely to change the diagnosis in patients who had imaging compared with control patients (e.g., 71% revised vs. 16%, p<0.001) and were more confident in their diagnosis (p<0.001). Clinicians were also more likely to change the diagnosis if the scan was abnormal than if it was normal (82% vs. 46%).

Kemp et al. conducted a retrospective study of the impact of DAT-SPECT on the clinical diagnosis and subsequent management of 80 consecutive patients with possible DLB. (32) 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 antipsychotic, dopaminergic, or cholinergic medication was changed in about half of the patients after the scan, although many (irrespective of the imaging results) were in the earliest phase of their disease process and did not require immediate treatment for symptoms. In addition, the small numbers did not allow substantive conclusions about changes in specific therapies.

Section Summary: Effect on Health Outcomes of DAT-SPECT in Patients With Clinically Uncertain DLB
Evidence of clinical utility includes 1 RCT that evaluated changes in diagnosis and confidence in diagnosis following DAT-SPECT imaging. This study indicates that DAT-SPECT can influence diagnosis of DLB, particularly when the scan is abnormal. It cannot be determined from this study whether the revised diagnosis was more accurate or resulted in a beneficial change in patient management. Longer follow-up of patients in this study may lead to greater certainty regarding the effect of this technology on health outcomes.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01950468*</td>
<td>Evaluation of the Diagnostic Efficacy and Safety of [123I]NAV5001 as an Imaging Agent to Aid in the Diagnosis of Parkinsonian Syndromes</td>
<td>275</td>
<td>Mar 2016</td>
</tr>
<tr>
<td>NCT01453127</td>
<td>DaTSCAN Imaging in Aging and Neurodegenerative Disease</td>
<td>130</td>
<td>Nov 2016</td>
</tr>
<tr>
<td>NCT01141023</td>
<td>The Parkinson's Progression Markers Initiative (PPMI)</td>
<td>680</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT01767818</td>
<td>Longitudinal, Single-center Prospective Study to Assess Progression of Clinical Features and Biologic Markers of Parkinson's Disease Subjects of Varying Levels of Disease Severity</td>
<td>240</td>
<td>Sep 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

Summary of Evidence
The evidence for dopamine transporter single-photon emission computed tomography (DAT-SPECT) in patients who have clinically uncertain Parkinson disease (PD) includes a number of studies from Europe, where a ligand has been available for over a decade. Relevant outcomes are test accuracy, symptoms, and functional outcomes. In terms of technical performance, the ligand is specific for the striatal dopamine transporter (DAT), and studies indicate reliability in assessment of the images when performed by experienced readers. Studies of diagnostic accuracy report good specificity for confirming nigrostriatal degeneration, with less sensitivity for ruling out
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 compared with the criterion standard of histopathologic diagnosis. Evidence on clinical utility includes a randomized controlled trial (RCT) that showed more patients evaluated with DAT-SPECT have changes in diagnosis and management than controls without imaging; however, there is limited evidence to evaluate whether these changes improve health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence on DAT-SPECT in patients who have clinically uncertain dementia with Lewy bodies (DLB) includes studies on diagnostic accuracy and its effect on diagnosis and confidence in diagnosis. Relevant outcomes are test accuracy, symptoms, and functional outcomes. For discriminating between DLB and Alzheimer disease, the sensitivity and specificity of DAT-SPECT is somewhat lower than for parkinsonian syndrome (PS), although the comparison standard used in the available studies may be flawed. Evidence on clinical utility includes an RCT that indicates that DAT-SPECT can influence diagnosis of DLB, particularly when the scan is abnormal. It cannot be determined from this study whether the revised diagnosis was more accurate or resulted in a beneficial change in patient management. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Clinical Input Received Through Academic Medical Centers and Specialty Medical Societies**

While the various Academic Medical Centers and Specialty Medical Societies may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the Academic Medical Centers or Specialty Medical Societies, unless otherwise noted.

**2015 Input**

In response to requests, input was received from 3 academic medical centers (4 reviewers) and 1 physician specialty society while this policy was under review in 2015. Input on whether DAT-SPECT is considered to be medically necessary in the assessment of clinically uncertain parkinsonian syndromes or to differentiate between clinically uncertain parkinsonian syndromes and essential tremor was mixed. A majority of respondents did not consider DAT-SPECT to be medically necessary to differentiate between DLB and Alzheimer's disease.

**2012 Input**

In response to requests, input was received from 3 academic medical centers (6 reviewers) and 3 physician specialty societies while this policy was under review in 2012. Input regarding the medical necessity of DAT-SPECT was mixed.

**Practice Guidelines and Position Statements**

**American College of Radiology**

The American College of Radiology (ACR) published appropriateness criteria for dementia and movement disorders in 2014. (33) ACR states that the diagnosis of idiopathic PD is usually based on patient history and physical examination alone and that when clinical signs and symptoms and response to medication are typical of PD, neuroimaging is not required. In patients with unusual clinical features, incomplete or uncertain medication responsiveness, or clinical diagnostic uncertainty, imaging to exclude alternative pathologies may be indicated. ACR states that PET and SPECT tracer studies exploring the presynaptic nigrostriatal terminal function and the postsynaptic dopamine receptors have been unable to reliably classify the various Parkinson syndromes and may not reliably measure disease progression. Use of DAT-SPECT was rated as “may be appropriate” to evaluate suspected dementia with Lewy bodies or Parkinson disease with either typical or atypical clinical features.

**American Academy of Neurology**

The 2006 practice parameters (reaffirmed in July 2013) from the American Academy of Neurology state that β-CIT and IBZM (iodobenzamide) SPECT are possibly useful in distinguishing PD from essential tremor (ET; 5 Class III studies). (34) There was insufficient evidence to determine if these modalities are useful in distinguishing PD from other forms of parkinsonism.
Society of Nuclear Medicine and Molecular Imaging
The international Society of Nuclear Medicine, now called the Society of Nuclear Medicine and Molecular Imaging, provided a practice guideline for DAT 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 presynaptic PS (PD, multiple-system atrophy, progressive supranuclear palsy). Other indications are the early diagnosis of presynaptic PS, differentiation of presynaptic PS from parkinsonism without presynaptic dopaminergic loss (e.g., drug-induced parkinsonism, psychogenic parkinsonism), and differentiation of DB 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.

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. (35) 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.

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. (36) 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 PS and for the differentiation of DB 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 region of interest.

National Institute for Health and Clinical Evidence
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. (37) The guideline states that 123I-FP-CIT SPECT should be considered for people with tremor where ET 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). This guideline is being updated.

NICE published a clinical guidelines on dementia in 2006. (38) 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 DB if the diagnosis is in doubt. This guideline is being updated.

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

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
19. Tolosa E, Borght TV, Moreno E. Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients...


Coding

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>78607</td>
<td>Brain imaging, tomographic (SPECT)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A9584</td>
<td>Iodine I-123 ioflupane, diagnostic, per study dose, up to 5 millicuries</td>
</tr>
</tbody>
</table>

Appendix

N/A

History

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/15/12</td>
<td>New policy. Policy created with literature review through March 2012; considered investigational.</td>
</tr>
<tr>
<td>09/27/13</td>
<td>Policy updated with literature review through May 28, 2013; references 19 and 23 added; policy statement unchanged.</td>
</tr>
<tr>
<td>09/23/14</td>
<td>Annual Review. Policy updated with literature review through June 6, 2014; reference 6 added; policy statement unchanged.</td>
</tr>
</tbody>
</table>

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2016 Premera All Rights Reserved.
Discrimination Is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at [https://ocrportal.hhs.gov/ocr/portal/lobby.jsf](https://ocrportal.hhs.gov/ocr/portal/lobby.jsf), or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action because of race, color, national origin, age, disability or sex.

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at [https://ocrportal.hhs.gov/ocr/portal/lobby.jsf](https://ocrportal.hhs.gov/ocr/portal/lobby.jsf), or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormacion. Daytoy a pakdaar mabalini nga adda ket naglaon iti napateg nga impormasion maianggeps iti aplikasyonno wennyo coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pelta iti daytoy a pakdaar. Mabalini nga adda rumbeng nga aramideny nga addang sakbay dagiti partikular a naitudd ng haal auldaw tapno mapagtalaineyدو التغطية وتقاسم التكاليف. لديك الحق في الاحتفاظ بالمعنوية أو تغطية محددة حتى بلوغ سن ال 65 سنة. أنت تتحمل على حسابك كاملة تكلفة التغطية. للاطلاع أكثر، يمكنك زيارة [http://www.hhs.gov/ocr/office/file/index.html](http://www.hhs.gov/ocr/office/file/index.html).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.
Chiama 800-722-1471 (TTY: 800-842-5357).
Japanese (Japanese): この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている情報が重要な日を確認してください。健康保険や有料サービスを維持するには、特定の期限内に行動を取りなければなりません。ご自身の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

Korean (Korean): 본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 귀하의 귀하와 건강 커버리지를 계약 유지하거나 변경을 결정하기 위해서 정정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 주요 귀하의 언어에 따라 비용 부담없이 알 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)으로 전화하시십시오。

Lao (Lao): ຄ່າທ່ານມີ ສິ ດໄດ້ຮັບຂໍ້ ແມ່ນນີ້ 800-722-1471 (TTY: 800-842-5357) ແລະ ການປະຕິບັດທ່ານໄດ້ຮັບ 800-842-5357. 

Punjabi (Punjabi): ਤੁਹਾਡੀ ਇਥ੍ਰੀਆਂ ਦੇ ਵਿਚ ਇਸ ਪ੍ਰੀਮਰ ਬਲ੍ਯਾਕ്സ ਦੇ ਖ਼ਬਰਾਂ ਦੀ ਬਹੁਤ ਮੁਦਰਾ ਜਾਂ ਇਹ ਤੁਹਾਡੀ ਸੰਸਕ੍ਰਿਤੀ ਤੇ ਪੁਰਾਣ ਦਿਨ ਦੀ ਅਕਸਰ ਹੁੰਦੀ ਹੈ। ਤੁਹਾਡੀ ਇਥ੍ਰੀਆਂ ਦੀ ਬਹੁਤ ਮੁਦਰਾ ਤੁਹਾਡੀ ਸਮਾਜ ਤੇ ਸਾਰਾ ਸੌਗਿਲ ਜੋ ਕਿ ਵੀ ਮੁਖੀ ਹੁੰਦੇ ਹਨ। ਤੁਹਾਡੀ ਇਥ੍ਰੀਆਂ ਦੀ ਬਹੁਤ ਮੁਦਰਾ ਤੁਹਾਡੀ ਗਹਵੇਰਾ ਦੀ ਅਕਸਰ ਹੁੰਦੀ ਹੈ। ਤੁਹਾਡੀ ਇਥ੍ਰੀਆਂ ਦੀ ਬਹੁਤ ਮੁਦਰਾ ਤੁਹਾਡੀ ਸਮਾਜ ਤੇ ਸਾਰਾ ਸਿੱਖਿਆ ਜੋ ਕਿ ਵੀ ਮੁਖੀ ਹੁੰਦੇ ਹਨ। ਤੁਹਾਡੀ ਇਥ੍ਰੀਆਂ ਦੀ ਬਹੁਤ ਮੁਦਰਾ ਤੁਹਾਡੀ ਸਮਾਜ ਤੇ ਸਾਰਾ ਸਿੱਖਿਆ ਜੋ ਕਿ ਵੀ ਮੁਖੀ ਹੁੰਦੇ ਹਨ। 


Russian (Russian): Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы можете иметь право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Spanish (Spanish): Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llámenos al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog): Ang Paunawa na ito ay nagalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring may mga mahalagang petsa dito sa paunawa. Maaring may mga mahalagang petsa dito sa paunawa. May karapatan ka na makakuha ng ganitong impormasyon para sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llámenos al 800-722-1471 (TTY: 800-842-5357).

Thai (Thai): ประกาศนี้มีข้อสำคัญที่ควรรู้กับการขอสิทธิ์ในประกันสุขภาพของคุณ Premera Blue Cross และการดำเนินการในกรณีที่คุณควรจะมี ด้านข่าวสารที่เกี่ยวกับสถานะที่เปลี่ยนแปลงจะส่งผลกระทบต่อการขอสิทธิ์ในประกันสุขภาพของคุณ คุณมีสิทธิที่จะได้รับข้อมูลและข่าวสารในภาษาของคุณได้ที่ 800-722-1471 (TTY: 800-842-5357).

Ukrainian (Ukrainian): Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує ймовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб забезпечити Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).