Uniform Medical Plan coverage limits
Updates effective 7/1/2017

The benefit coverage limits listed below apply to these UMP plans:
Uniform Medical Plan Classic (UMP Classic)
UMP Consumer-Directed Health Plan (UMP CDHP)
- UMP Plus–Puget Sound High Value Network
- UMP Plus–UW Medicine Accountable Care Network

Some services listed under these benefits have coverage limits. These limits are either determined by a Health Technology Clinical Committee (HTCC) decision or a Regence BlueShield medical policy. The table below does not include every limit or exclusion under this benefit. For more details, refer to your plan’s Certificate of Coverage.

### Radiology

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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
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| Virtual Colonoscopy, CT Colonography (PDF) | Regence Medical Policy Rad36 | • 74261, 74262  
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### Radiology Quality Initiative

We have partnered with AIM Specialty Health to administer our Radiology Quality Initiative (RQI) program and full utilization management for our members. View program requirements at https://www.regence.com/radiology-quality-initiative.

- Phone 1 (877) 291-0509

Check for specific HTCC pre-authorization requirements documented under Cardiac Nuclear Imaging and Imaging for Rhinosinusitis.

Contact AIM to obtain an order number for the following codes:
* Effective September 1, 2017: UMP is subject to HTCC decision: 70554, 70555, 78607, 78608. Functional neuroimaging for primary degenerative dementia or mild cognitive impairment is not a covered benefit for 70554, 70555, 78607, 78608.
Dopamine Transporter Single-Photon Emission Computed Tomography

**Effective:** March 1, 2017

**Next Review:** January 2018

**Last Review:** January 2017

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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

Dopamine transporter single-photon emission computed tomography (DAT-SPECT) detects presynaptic dopaminergic deficit by measuring DAT binding. In general, striatal DAT binding is reduced in certain neurological conditions, while striatal DAT binding is in the normal range in others. Therefore, use of DAT-SPECT is being proposed to improve differential diagnosis between certain types of neurological conditions.

**MEDICAL POLICY CRITERIA**

**NOTE:** This policy only addresses SPECT when used with dopamine transporter ligands for diagnosing specific neurological disorders. Use of SPECT that does not incorporate these ligands is currently addressed in another commercial policy (please see Cross References below).

Dopamine transporter 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;

OR
distinguishing between parkinsonian syndromes and essential tremor; OR
• distinguishing between dementia with Lewy bodies and Alzheimer disease; OR
• monitoring of disease progression.

**NOTE:** A summary of the supporting rationale for the policy criteria is at the end of the policy.

## CROSS REFERENCES

1. Magnetoencephalography/Magnetic Source Imaging (MSI), Radiology, Policy No. 22
2. Magnetic Resonance Spectroscopy, Radiology, Policy No. 27
3. Single Photon Emission Computed Tomography (SPECT) for the Diagnosis of ADHD, Dementias and Other Psychiatric Conditions, Radiology, Policy No. 44
4. Biochemical Markers of Alzheimer's Disease, Laboratory, Policy No. 22
5. Deep Brain Stimulation, Surgery, Policy No. 84
6. Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders, Medicine, Policy No. 148

## 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.\(^1\) 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 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.\(^2\) 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. There is, however, a significant percentage of patients with clinically diagnosed PD who do not show reduced DAT-SPECT binding. These are commonly referred to as scans without evidence of dopaminergic deficit. Additional research may shed light on these cases.\(^3\)

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, semiquantitative, or quantitative. Because patients typically do not become symptomatic before a substantial number of striatal synapses have degenerated, visual interpretation of the scan is thought to be sufficient for clinical evaluation. A variety of methods are being tested to improve the validity and reliability of ratings, including commercially available software to define the region of interest (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.[4] Semiquantitative analysis also requires normal control values and varies across imaging systems.

Dopamine transporter ligands include $^{123}$I-$\beta$-CIT, $^{123}$I-FP-CIT, and 99mTc-TRODAT-1. $^{123}$I-$\beta$-CIT requires a delay between injection and scan of about 24 hours. $^{123}$I-FP-CIT (DaTscan™) is a fluoropropyl derivate of $\beta$-CIT that can be injected three to six 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 as a new molecular entity (NME) 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.”

EVIDENCE SUMMARY

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

1. Analytic validity (technical feasibility) is demonstrated, including reproducibility and precision. For comparison among studies, a common standardized protocol for the new diagnostic technology is established.

2. Clinical validity (diagnostic accuracy) - sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) compared to standards are established in relevant populations of patients, such as those with suspected early Parkinson disease (PD) or inconclusive diagnosis.

3. Clinical utility of a diagnostic technique, i.e., how the results of the study can be used to benefit patient management, is established. The clinical utility of both positive and negative tests must be established. The 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 nondegenerative disorders that present with similar symptoms, and to discriminate dementia with Lewy bodies (DLB) from Alzheimer disease (AD).

The analytic validity of DAT-SPECT is the same, regardless of the indication it is used for, therefore in the evidence summary below, only clinical validity and utility are addressed separately for each indication.

**ANALYTIC VALIDITY**

DAT-SPECT is based on the selective affinity of ligands for the DAT and the exclusive location of the DAT in dopamine synthesizing neurons.\(^5\) 123I-β-CIT is a cocaine analog that has a high affinity to the DAT and serotonin transporters. 123I-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 antiparkinsonian 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.

In 2014, Seibyl et al. reported intra- and interrater agreement for DAT-SPECT images with data from five multicenter trials (818 patients).\(^6\) DAT binding was classified as “normal” or “abnormal.” Within-reader agreement was assessed in one 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.

A 2012 study evaluated interobserver variability in the visual interpretation of DAT-SPECT.\(^7\) Eighty-nine previously obtained DAT-SPECT scans were blindly reviewed by three 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 three observers achieved a sensitivity of 100%, with specificities of 89-96%.

**Section Summary**

Preclinical studies to determine the analytical validity of DAT-SPECT report 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. The analytic validity of DAT-SPECT is the same, regardless of the indication it is used for, therefore in the evidence summary below, only clinical validity and utility are addressed in the following evidence sections.

PARKINSONIAN SYNDROMES

Clinical Validity

The most informative evaluation of clinical validity requires prospective, independent, and blinded assessment of test results compared with a criterion standard in an appropriate population.

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.\(^8\) 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 criteria-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.

In 2009 Marshall et al., reported a prospective, investigator-initiated industry-funded, 36-month European multicenter study with repeat DAT-SPECT and criterion standard clinical diagnosis (video at 36 months by two movement disorders specialists) in 99 diagnostically uncertain cases of PD or essential tremor (ET).\(^9\) Patients with other potential causes of parkinsonism/tremor and patients with major comorbid illness were excluded; three 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 three 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 three blinded 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 range, 0.94-0.97).
At 36 months 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 three years of the study. These cases are referred to as SWEDDS (Subjects with Scans Without Evidence of Dopamine Deficiency). DAT-SPECT did not improve diagnostic accuracy in the SWEDDS patients at the 36-month clinical assessment. Although this study indicates that an abnormal DAT-SPECT scan may help to confirm a clinical diagnosis of PD in the majority of patients, the low NPV suggests that a normal DAT-SPECT scan cannot be used to rule out disease and thus may not be helpful in preventing the potential clinical overdiagnosis of PD.

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. These studies are described below.

In 2014 Brigo et al. reported a meta-analysis of DAT-SPECT to differentiate between PD and vascular or drug-induced parkinsonisms.[10] The meta-analysis included five studies that had diagnosis confirmed by imaging. There were a number of study limitations, most notably, in three 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..[11] The studies included 92 patients with clinically uncertain parkinsonian syndromes (CUPS) at baseline who had confirmed clinical diagnosis at one year. Bajaj et al. assessed the effect of age, disease stage, and other clinical and neurocognitive measures on the diagnostic performance of DAT-SPECT.[12] Hauser et al. reported that the diagnostic accuracy of DAT-SPECT was higher than clinical diagnosis at baseline.[13] Both studies are limited because clinical diagnosis at one 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. These studies are described below.

In 2014, O'Brien et al. published an industry-funded pooled analysis of four clinical studies that were submitted in support of the new drug application to the U.S. Food and Drug Administration (FDA).[14] 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 three 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 two studies included a population of patients with an uncertain diagnosis, one of which was an open-label phase VI 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 postsynaptic dopamine receptor binding in 248 patients with unclassified PS in 2008. 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 two standard deviations above or below healthy controls considered abnormal. Using clinical diagnosis as the comparator, DAT-SPECT was able to distinguish between PD and ET (odds ratio [OR] = 82); between PD and vascular parkinsonism (OR=61); between PD and drug-induced parkinsonism (OR=36); and between PD and atypical PS (OR=1).

In 2000, Benamer et al. conducted a multicenter study that 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 five 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.

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. 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 five years and 88% PPV in patients with disease duration of five years or more.

Joutsa et al. reported a retrospective study of the diagnostic accuracy of PD by general neurologists. 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 25% of diagnoses by general neurologists were incorrect.

Section Summary

The literature on the clinical validity of DAT-SPECT to diagnose and distinguish Parkinsonian syndromes 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 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 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.\textsuperscript{[11,19]} Criteria of uncertainty included at least one of the following: only one of the three cardinal signs of parkinsonism; two 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 one 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%, \textit{p}=0.002). This was due to a greater change in management by movement disorder specialists (51% DAT-SPECT vs 28% controls, \textit{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. 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 (\textit{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.

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 reexamined by two neurologists who were blinded to the original diagnosis (overall agreement between the two, 75.7%; κ=0.461). Patients then underwent DAT-SPECT imaging, which was evaluated by two masked independent and experienced nuclear medicine physicians using a semiquantitative approach and classified as normal or abnormal (κ=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 six patients (9.8%) diagnosed at their center. All patients were reexamined by two 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 two experienced nuclear medicine physicians using a semiquantitative 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.

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.[21,22] Criteria of uncertainty were assessed by referring neurologists and included at least one of the following: only one of the three cardinal signs of parkinsonism, with or without asymmetry; two 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 recategorized and 16 of 118 patients (14%) were recategorized 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 two years, 85 patients (72%) were available for follow-up.[22] In eight 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
nonpresynaptic 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 five of these six, the initial scan was considered abnormal. The second DAT-SPECT results helped to establish a diagnosis in seven of eight patients (87.5%) with a previously inconclusive diagnosis.

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.[23-26]

Oravivattanakul et al. reported on the concordance between pre-scan diagnosis and scan results in 175 CUPS patients who were seen by movement disorders neurologists.[26] When essential/dystonic tremor was suspected, the scan was normal in 79%. DaTscan influenced medical treatment more when scans were abnormal than when normal. Only 4% of patients with abnormal scans remained off medications, while 24% of patients with normal scans remained on medication.

Sadasivan and Friedman also reported on the clinical outcome of the change in management.[25] 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.

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.[27] 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).

A 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.[24] 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, Siefert and Weiner found that confidence in a diagnosis of PD or non-PD was significantly increased with abnormal scans, but not with normal scans.[28] For many patients, the scan confirmed the diagnosis of PD, despite a poor response to medication and resulted in a change in medication.

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.[29,30]

Section Summary

Evidence on clinical utility of DAT-SPECT includes one well-conducted RCT, a prospective multicenter trial, and several retrospective studies that have evaluated the effect of DAT-SPECT on diagnosis of CUPS and subsequent 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 (eg, medication management). However, there is only one 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 imaging; however, no improvement in quality of life was observed by the 1-year follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

DEMENTIA WITH LEWY BODIES

Clinical Validity

A 2015 meta-analysis by Brigo et al. evaluated the diagnostic accuracy of DAT-SPECT to distinguish between DLB and other dementias.[31] Eight studies were included, of which three studies used histopathology as the reference standard. Studies that used clinical diagnosis as the reference standard showed diagnostic accuracy between 84-86% (ten studies) when using visual or semiquantitative analysis. The two studies using a histopathologic reference standard and visual analysis showed similar sensitivity (87%) and slightly higher specificity (92%) compared with studies that used clinical diagnosis as the reference standard. The single study that used semiquantitative analysis with histopathology as a reference standard correctly identified the 15 patients with DLB (100% sensitivity) and had 90% specificity in the identification of the eight patients with non-DLB dementia. Because only 23 patients enrolled in this study, additional research is needed to corroborate these results.

Papathanasiou et al. reported a meta-analysis of the diagnostic accuracy of DAT-SPECT in DLB in 2012.[32] 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 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 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%.

The largest study to evaluate the diagnostic accuracy of 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). In 28 patients, no diagnosis was made. The diagnoses were established by a consensus panel of three clinicians who did not have access to DAT-SPECT results, and DAT-SPECT scans were assessed visually by three 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.

Several studies have followed patients with inconsistent results from DAT-SPECT and clinical diagnosis.

Van der Zande et al (2016) reported on seven (10.4%) of 67 patients who were clinically diagnosed with DLB but had normal scans. In five of the seven, second DAT-SPECT scans (average 1.5 years later) were abnormal. There were no differences in baseline clinical characteristics, but patients with initially normal scans were less severely affected after one year. This study evaluated small numbers of subjects and lacked autopsy findings to confirm the diagnosis.

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

Clinical Utility

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. 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 one core feature or one 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 one 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 (eg, 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.[37] 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 postscan working clinical diagnosis of DLB (90%), one had a diagnosis of vascular dementia (5%), and one 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

Evidence of clinical utility includes one 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.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF RADIOLOGY

The American College of Radiology (ACR) published appropriateness criteria for dementia and movement disorders in 2015.[38] 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 positron emission tomography and SPECT tracer studies exploring the presynaptic nigrostriatal terminal function and the postsynaptic dopamine receptors have been unable to reliably classify the various PSs and may not reliably measure disease progression. Use of DAT-SPECT was rated as “may be appropriate” to evaluate suspected DLB or PD 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). There was insufficient evidence to determine if these modalities are useful in distinguishing PD from other forms of Parkinsonism.

**MOVEMENT DISORDERS SOCIETY**

The Movement Disorder Society’s (MDS) diagnostic criteria for PD from 2015 are intended for use in clinical research but may be used to guide clinical diagnosis. MDS considers clinical expert opinion to be the criterion standard to diagnose PD and that diagnoses are usually made clinically without need for ancillary diagnostic testing. Methods that may become available as knowledge advances are diagnostic biochemical markers, anatomical neuroimaging, and methods to detect alpha-synuclein deposition. MDS noted that, although dopaminergic neuroimaging can help to distinguish parkinsonism from PD mimics like ET, “it does not qualify as a criterion for the differentiation of PD from other parkinsonian conditions like atypical parkinsonian syndromes.”

**SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING**

The Society of Nuclear Medicine and Molecular Imaging (previously known as the International Society of Nuclear Medicine), provided a practice guideline for DAT imaging with SPECT in 2011. 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). However, the pattern of \(^{123}\)I-ioflupane uptake cannot discriminate between the latter disorders with any high degree of accuracy.

Other indications are the early diagnosis of presynaptic PS, differentiation of presynaptic PS from parkinsonism without presynaptic dopaminergic loss (eg, drug-induced parkinsonism, 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.

**SUMMARY**

There is not enough research to show that there are improved health outcomes as a result of diagnosis using DAT-SPECT compared to standard clinical diagnosis for any indication. In addition, there are no research-based clinical guidelines that recommend the use of DAT-SPECT over the current standard clinical diagnosis for any indication. Therefore, the use of dopamine transporter single-photon emission computed tomography (DAT-SPECT) is considered investigational for all indications.

**REFERENCES**


21. Catafau, AM, Tolosa, E. Impact of dopamine transporter SPECT using 123I-ioflupane on diagnosis and management of patients with clinically uncertain Parkinsonian


34. van der Zande, JJ, Booij, J, Scheltens, P, Raimakers, PG, Lemstra, AW. [(123)]FP-CIT SPECT scans initially rated as normal became abnormal over time in patients with probable dementia with Lewy bodies. European journal of nuclear medicine and molecular imaging. 2016 Jun;43(6):1060-6. PMID: 26830298


## CODES

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*Date of Origin: January 2016*
Magnetoencephalography/Magnetic Source Imaging (MEG/MSI)

Effective: July 1, 2017

Next Review: June 2018
Last Review: June 2017

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Magnetoencephalography (MEG) is a noninvasive functional imaging technique in which the weak magnetic forces associated with the electrical activity of the brain are recorded externally on the scalp.

MEDICAL POLICY CRITERIA

I Magnetoencephalography and magnetic source imaging may be medically necessary for the following indications:
   A For the purpose of determining the laterality of language function, as a substitute for the Wada test, in patients being prepared for surgery for epilepsy, brain tumors, and other indications requiring brain resection
   B As part of the preoperative evaluation of patients with intractable epilepsy (seizures refractory to medical therapy) when standard techniques, such as MRI and EEG, do not provide satisfactory localization of epileptic lesion(s).

II Magnetoencephalography and magnetic source imaging are considered investigational for all other indications, including but not limited to the following:
   A Autism spectrum disorder (ASD)
NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Single Photon Emission Computed Tomography (SPECT) of the Brain, Radiology, Policy No. 44
2. Dopamine Transporter Single-Photon Emission Computed Tomography, Radiology, Policy No. 57

BACKGROUND

Using mathematical modeling, the recorded data are then analyzed to provide an estimated location of the electrical activity. This information can be superimposed on an anatomic image of the brain, typically a magnetic resonance imaging scan (MRI), to produce a functional/anatomic image of the brain, referred to as magnetic source imaging or MSI. The primary advantage of MSI is that while the conductivity and thus the measurement of electrical activity as recorded by the electro-encephalogram (EEG) is altered by surrounding brain structures, the magnetic fields are not. This results, for instance, in better spatial localization of epileptic foci detected by MEG as compared with surface EEG, which can produce distorted signals. However, MEG has some limitations as well, since magnetic fields generated deep within brain tissues decay rapidly over distance and may be less likely to be detected at the surface compared with electrical fields. Therefore, surface EEG and MEG are often considered complimentary technologies.

The technique itself is extremely sophisticated. Detection of the weak magnetic fields depends on gradiometer detection coils coupled to a superconducting quantum interference device (SQUID), which in turn requires a specialized room, shielded from other magnetic sources. Mathematical modeling programs based on idealized assumptions are then used to translate the detected signals into functional images. In its early evolution, clinical applications were limited by the use of only one detection coil requiring lengthy imaging times, which, because of body movement, were also difficult to coordinate with the MRI. However, more recently the technique has evolved to multiple detection coils arranged in an array that can provide data more efficiently over a wide extracranial region.

One clinical application is localization of the pre- and postcentral gyri as a guide to surgical planning in patients scheduled to undergo neurosurgery for epilepsy, brain neoplasms, arteriovenous malformations, or other brain disorders. These gyri contain the “eloquent” sensorimotor areas of the brain involved in sensory, motor or language function. The preservation of these areas is considered critical during any type of brain surgery. In normal situations, these areas can be identified anatomically by MRI, but frequently the anatomy is distorted by underlying disease processes. In addition, the location of eloquent functions is variable even among healthy patients. Therefore, localization of eloquent cortex often requires such intraoperative invasive functional techniques as cortical stimulation under local anesthesia or somatosensory-evoked responses on electrocorticography (ECoG). While these
techniques can be done at the same time as the planned resection, they are cumbersome and can add up to 45 minutes of anesthesia time. Furthermore, sometimes these techniques can be limited by the small surgical field. An additional presurgical test that is often used to localize the eloquent hemisphere is the intracarotid amobarbital test (Wada test). MEG/MSI has been proposed as a substitute for the invasive Wada test.

Another related clinical application of MEG/MSI is localization of epileptic foci, particularly for screening of surgical candidates and surgical planning. Alternative techniques include MRI, positron emission tomography (PET), or single photon emission computed tomography (SPECT) scanning. Anatomic imaging (i.e., MRI) is effective when epilepsy is associated with a mass lesion, such as a tumor, vascular malformations, or hippocampal atrophy. If an anatomic abnormality is not detected, patients may undergo a PET scan. In a small subset of patients, extended electrocorticography (ECoG) or stereotactic electroencephalography (SEEG) with implanted electrodes are considered the gold standards for localizing epileptogenic foci. MEG/MSI was principally investigated as an alternative to invasive monitoring.

MEG is also being studied as a method for identifying and evaluating abnormalities of neurological functioning in the brain in a number of other conditions such as schizophrenia, bipolar disorder, post-traumatic stress disorder (PTSD), autism spectrum disorder (ASD), acute migraine headache, and dementias.

MSI has also been used as a research tool in the investigation of dyslexia, psychiatric disorders, functional evaluation of the gastrointestinal tract, diagnosis of mesenteric ischemia, and evaluation of uterine contractions in pregnancy.

EVIDENCE SUMMARY

Ideally, randomized trials comparing the outcomes of patients who received magnetoencephalography (MEG) as part of their diagnostic workup compared with patients who did not receive MEG could determine whether MEG improves patient outcomes. However, it is unlikely that randomized trials will ever be available due to the small number of patients who require this testing. Consequently, almost all of the studies evaluating MEG have been retrospective studies, where MEG, other tests, and surgery have been selectively applied to patients. Since patients often drop out of the diagnostic process before having intra-cranial electroencephalogram (IC-EEG), and many patients ultimately do not undergo surgery, most studies of associations between diagnostic tests and between diagnostic tests and outcomes are irreparably biased by selection and ascertainment biases. For example, studies evaluating the correlation between MEG and IC-EEG invariably did not account for the fact that MEG information was used to deselect a patient from undergoing IC-EEG. In addition, IC-EEG findings only imperfectly correlated with surgical outcomes, meaning that it was an imperfect reference standard.

In light of these obstacles to high quality evidence, the focus of this literature review was on whether there are consistent findings in nonrandomized studies to suggest associations between MEG findings and other noninvasive and invasive diagnostic tests and between MEG findings and surgical outcomes.

LOCALIZATION OF SEIZURE FOCUS

Systematic Reviews
This section was initially based on a 2008 BlueCross BlueShield Association Technology Evaluation Center (TEC) Special Report reviewing the evidence regarding MEG for localization of epileptic lesions.[1] MEG has been proposed as a method for localizing seizure foci for patients with normal or equivocal MRI and negative video-EEG examinations, so-called “nonlesional” epilepsy. Such patients often undergo MEG, positron emission tomography (PET), or ictal-SPECT (single photon emission computed tomography) tests to attempt to localize the seizure focus. They then often undergo invasive IC-EEG, a surgical procedure in which electrodes are inserted next to the brain. MEG would be considered useful if, when compared to not using MEG, it improved patient outcomes. Such improvement in outcomes would include more patients being rendered seizure-free, use of a less invasive and morbid diagnostic workup, and increased surgical success rates. This is a complicated array of outcomes that has not been thoroughly evaluated in a comprehensive manner.

Lau and colleagues performed a meta-analysis of 17 studies that correlated MEG findings to surgical outcomes. In this meta-analysis, sensitivity and specificity had unorthodox definitions.[2] Sensitivity was defined as the proportion of patients cured with surgery, in whom the MEG-defined epileptic region was resected, and specificity was the proportion of patients not cured with surgery in whom the MEG-defined epileptic region was not resected. The pooled sensitivity was 0.84, meaning that among the total number of cured patients, 14% occurred despite the MEG-defined region not being resected. Pooled specificity was 0.52 meaning that among the 48% of patients not cured the MEG-localized region was resected. These results are consistent with an association between resection of the MEG-defined region and surgical cure, but it is an imperfect predictor of surgical success. The analysis did not address the question of whether MEG contributed original information to improve the probability of cure.

Nonrandomized Studies

A representative study of MEG by Knowlton and colleagues demonstrated many of the problematic issues of evaluating MEG.[3] In this study of 160 patients with nonlesional epilepsy, all had MEG, but only 72 proceeded to IC-EEG. The calculations of diagnostic characteristics of MEG were biased by incomplete ascertainment of the reference standard. However, even examining the diagnostic characteristics of MEG using the 72 patients who underwent IC-EEG, sensitivities and specificities were well below 90%, indicating the likelihood of both false-positive and false-negative studies. Predictive values based on these sensitivities and specificities mean that MEG can neither rule in nor rule out a positive IC-EEG, meaning that MEG cannot be used as a triage test before IC-EEG to avoid the potential morbidity in a subset of patients.

In a more recent study by Knowlton et al. of 77 patients who were recommended to have IC-EEG, MEG results modified the placement of electrodes in 18 cases.[4] Seven cases out of the 18 had positive intracranial seizure recordings involving the additional electrodes placed because of the MEG results. It was concluded that four patients are presumed to have had surgery modified as a result of the effect of MEG on altering the placement of electrodes. Surgical outcomes for these 4 patients are not reported. In this type of study, it is difficult to know how the patients would have been treated in the absence of the MEG results. It is stated that there was no additional morbidity resulting from the additional electrode placement. The study is not conclusive regarding the improvement in health outcomes due to use of MEG to alter electrode placement.
A study by Albert et al reviewed a series of pediatric patients undergoing surgery for epilepsy who had only undergone noninvasive monitoring prior to surgery.\(^5\) MEG was proposed to have avoided the need for the morbidity associated with invasive monitoring. Of 16 patients, 62.5% were seizure-free following surgery, and 20% experienced improvement. Two cases required additional surgery with invasive monitoring. Although most patients improved, it cannot be determined whether the outcomes were equivalent to the standard practice of pre-resection invasive monitoring.

A study by Wang et al compared 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) and MEG in identifying the epileptogenic zone, using invasive monitoring as the reference standard.\(^6\) FDG-PET identified the zone in 8 (50%) of patients and MEG identified the zone in 12 (75%) of patients. Although MEG was more sensitive than FDG-PET in this study, it still missed epileptogenic areas identified by invasive monitoring.

Another recent study by Koptelova et al compared MEG with video EEG monitoring in 22 patients.\(^7\) Of 75 “irritative” zones identified in the 22 patients by either method, a higher proportion was identified by MEG. Note that there is no true reference standard in this type of analysis. However, in analyses of intraoperative EEG, several zones identified only with this method were only identified by MEG, confirming to some extent increased sensitivity over video EEG. These recent studies suggest clinical utility for MEG in evaluation of epilepsy patients, but, due to the aforementioned problems, firm conclusions about the clinical utility of MEG cannot be determined.

A study by Nissen evaluated 382 recordings of complex epilepsy patients with inconclusive findings prior to MEG for localization of the epileptogenic zone (e.g., concordant tumor and EEG location).\(^8\) The authors concluded that “MEG localization ability cannot be predicted upfront, although the odds of a recording with MEG location were significantly higher in the absence of a tumor and in the presence of widespread MRI abnormalities.”

**LOCALIZATION OF ELOQUENT AND SENSORIMOTOR AREAS**

**Laterality of Language Function**

The determination of the laterality of the language function is important in determining the suitability of a patient for surgery and what types of additional functional testing might be needed prior to or during surgery. The Wada test is a standard method of determining hemispheric dominance for language. However, it is an invasive test that requires catheterization of the internal carotid arteries, which carries the risk of complications. If MEG provided concordant information with the Wada test, then MEG could be a noninvasive substitute for the Wada test.

Several studies have shown high concordance between the Wada test and MEG. For example, in the largest study by Papanicolaou and co-workers among 85 patients, there was concordance between the MEG and Wada tests in 74 (87%).\(^9\) In no cases were the tests discordant in a way that the findings were completely opposite. The discordant cases occurred mostly where the Wada test indicated left dominance and the MEG indicated bilateral language function. In an alternative type of analysis where the test was being used to evaluate the absence or presence of language function in the side in which surgical treatment was being planned, using the Wada procedure as the gold standard, MEG was 98% sensitive and 83% specific. Thus, if the presence of language function in the surgical site required intraoperative mapping and/or a tailored surgical approach, use of MEG rather than Wada
would have “missed” one case where such an approach would be needed, and resulted in five cases in which such an approach was unnecessary (false-positive MEG). It should be noted, however, that the Wada test is not a perfect reference standard, and some discordance may reflect inaccuracy of the reference standard.

**Mapping Sensorimotor Areas**

MEG may also be used for mapping the sensorimotor area of the brain to avoid such areas in the surgical resection area. Intraoperative mapping just before resection is generally done as the reference standard. Preoperative mapping as potentially done by MEG might aid in determining the suitability of the patient for surgery, or for assisting in the planning of other invasive testing.

Similar to the situation for localization of epilepsy focus, the literature is problematic in terms of evaluating the comprehensive outcomes of patients due to ascertainment and selection biases. Recent literature on the use of MEG in localizing the sensorimotor area provided only indirect evidence of utility. Studies tended to be limited to correlations between MEG and intraoperative mapping. The intraoperative mapping would be performed anyway in most resection patients.

A study by Niranjan et al. reviewed the results of 45 patients in whom MEG was used for localizing somatosensory function.[10] In 32 patients who underwent surgery, surgical access routes were planned to avoid regions identified as somatosensory by MEG. All patients retained somatosensory function. It is unknown to what extent MEG provided unique information not provided by other tests. In a study by Tarapore et al., 24 patients underwent MEG, transcranial magnetic stimulation, and intraoperative direct cortical stimulation to identify the motor cortex.[11] MEG and navigated transcranial magnetic stimulation were both able to identify several areas of motor function, and the median distance between corresponding motor areas was 4.71 mm. When comparing MEG to direct cortical stimulation the median distance between corresponding motor sites (12.1 mm) was greater than the distance between navigated transcranial magnetic stimulation and direct cortical stimulation (2.13 mm). This study cannot determine whether MEG provided unique information that contributed to better patient outcomes.

**OTHER INDICATIONS**

**Nonrandomized Studies**

Alhourani (2016) published a study that evaluated functional connectivity during resting state in 24 mild traumatic brain injury (mTBI) patients.[12] The goal was to determine if MEG could detect changes in neural communications causing cognitive deficits. Nine patients were evaluated by magnetoencephalography (MEG) and the remaining 15 were in a control group. The authors concluded that although MEG is a good tool for detecting diminished functional connectivity for mTBI patients; MEG warrants additional exploration.

Additional preliminary feasibility studies have been published in which MEG has been used to identify and evaluate abnormalities of neurological functioning in the brain in a number of other conditions such as schizophrenia[13], bipolar disorder[14], post-traumatic stress disorder (PTSD)[15], autism spectrum disorder (ASD)[16,17], migraine headache[18], and dementias[19].
PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF NEUROLOGY (AAN)

- In 2013 the AAN published a MEG model policy for presurgical evaluation of the following:[20]
  - To identify and localize area(s) of epileptiform activity in patients with intractable focal epilepsy when other diagnostic techniques are inconclusive
  - To identify, localize, and preserve eloquent cortex during resection surgery for brain tumors and vascular malformations

The limitations noted for MEG are that it cannot replace but may guide intracranial EEG placement and it is not a stand-alone test or the first order of test, but is one of several presurgical investigative technologies.

AMERICAN COLLEGE OF RADIOLOGY (ACR)[21]

A 2014 update of the ACR consensus-based practice guideline for seizures and epilepsy stated that only EEG using either scalp or intracranial electrodes and MEG “directly measure the brain’s electrical activity. As such, they could or should be the gold standard for localization.” In addition, the guideline stated that both EEG and MEG offer significantly higher temporal resolution than PET, ictal SPECT, and functional magnetic resonance imaging (fMRI). Below are the guideline conclusions for the role of MEG/MSI for preoperative diagnostic workup in surgical candidates with medically refractory epilepsy and/or for other surgical planning. In this patient population, MEG/MSI:

- May identify the ictal onset zone (IOZ) in nonlesional patients (normal MRI)
- Can provide confirmatory localization information for IOZ localization for potential lesions seen on MRI
- May help distinguish among multiple potential seizure foci in certain patients
- May guide placement of iEEG
- May substitute for invasive testing
- May be useful when other tests are discordant
- Is not a frontline or stand-alone tool
- Has the most value in the hands of experienced users in epilepsy referral centers

THE AMERICAN CLINICAL MAGNETOENCEPHALOGRAPHY SOCIETY (ACMEGS)[22]

In a 2011 consensus-based practice guideline on preoperative functional brain mapping using magnetic evoked fields, the ACMEGS listed the following indications for MEG evoked fields:

- Localization of somatosensory cortex, and primary motor, auditory, and visual cortices
- Localization of the central sulcus in conjunction with motor evoked fields
- Biologic quality check of coordinate transformation (spatial biocalibration)
- Determining the language-dominant hemisphere in patients with either organic or functional brain diseases before surgical interventions
- Objective functional evaluation of language processing (i.e., identification of location and latencies)
SUMMARY

Though the evidence is limited, magnetoencephalography/magnetic source imaging (MEG/MSI) has evolved to a standard of care as a noninvasive substitute for the Wada test in preoperative brain mapping in selected surgical candidates. In addition, clinical practice guidelines that address MEG/MSI consistently consider this imaging to add valuable information to conventional MRI and EEG. Therefore, MEG/MSI are considered medically necessary in carefully selected patients, who meet the medial policy criteria. There is not enough research to show that magnetoencephalography/magnetic source imaging (MEG/MSI) improves health outcomes for any other indication. Therefore, MEG/MSI is considered investigational for all other indications.

REFERENCES


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*Date of Origin: November 1997*
Single Photon Emission Computed Tomography (SPECT) of the Brain

Effective: May 1, 2017

Next Review: March 2018
Last Review: April 2017

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

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DESCRIPTION

Single photon emission computed tomography (SPECT) is a nuclear imaging technique that is used to visualize functional information about body organs, including the brain.

MEDICAL POLICY CRITERIA

Note:

- This policy addresses only single photon emission computed tomography (SPECT) of the brain. This policy does not address the use of SPECT other than SPECT of the brain.
- This policy does not address the use of dopamine transporter (DAT)-SPECT. Please refer to the Cross References below for the health plan commercial policy on DAT-SPECT.

Single photon emission computed tomography (SPECT) of the brain is considered investigative for the following conditions:

A Behavioral health disorders (including, but not limited to bipolar disorder, major depressive disorder, schizophrenia, and personality disorders)
B Attention-deficit/hyperactivity disorder (ADHD)
C Substance-related disorders (including alcohol)
D Autism
E Traumatic brain injury
F Cerebrovascular disease (including stroke, transient ischemic attack, and subarachnoid hemorrhage)
G Encephalopathy (including but not limited to Lyme, Wernicke’s, hypoglycemia, and hypoxic-ischemic encephalopathy)
H Chronic fatigue syndrome
I Dementias (including Alzheimer’s, vascular dementia, frontal temporal dementia, Pick’s disease and dementia with Lewy bodies)
J Parkinsonian syndromes and essential tremor
K Motor neuron disorders [including amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis, and progressive (spinal) muscular atrophy]
L Multiple sclerosis

II SPECT of the brain for indications other than those listed above may be considered medically necessary.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES
1. Magnetoencephalography/Magnetic Source Imaging (MSI), Radiology, Policy No. 22
2. Dopamine Transporter Single-Photon Emission Computed Tomography, Radiology, Policy No. 57

BACKGROUND

Brain imaging requires the use of radiopharmaceuticals that cross the blood-brain barrier. The radioactive isotope decay results in emission of gamma rays that are detected by a gamma camera which allows reconstruction of cross-sectional slices.

SPECT has been used to determine dopamine and serotonin receptor availability and to study regional cerebral blood flow in the brain. Because cerebral blood flow correlates with brain metabolism, the images provide information regarding which regions of the brain are affected, which in turn aids with differential diagnosis. In addition, SPECT has been proposed as a tool to diagnose and estimate treatment response in attention deficit/hyperactivity disorder (ADHD), Alzheimer’s disease /dementias, and other psychiatric conditions, such as major depression.

REGULATORY STATUS

There are a number of radiopharmaceutical agents that have been approved by the U.S. Food Drug Administration (FDA) for use with SPECT for a variety of indications. Some of these include:
- Adreview (iobenguane sulfate I-123)
- Technetium TC-99m (mebrofenin)
- I-123 isopropyliodoamphetamine (IMP, Spectamine)
- Tc-99m HMPAO (hexamethyl propylamine oxime, Ceretec)
- Tc-99m ECD (ethyl cysteinate dimer, Neurolite)
- thallium 201 diethyldithiocarbamate (T1-DDC)

**EVIDENCE SUMMARY**

The most rigorous evaluation of the impact of a diagnostic test on clinical outcomes is a randomized controlled trial (RCT) that evaluates health outcomes in patients who receive the new diagnostic test compared with patients who are evaluated without the new test and according to standard of care. Evidence from RCTs are necessary in order to establish how SPECT may be used in the clinical setting to either diagnose or direct treatment.

A significant number of published studies have focused on investigating pathologic differences in regional cerebral perfusion, for the purpose of diagnosis of disease, in response to drug therapy or for the evaluation of brain function for a number of neurological, psychiatric, and neurodegenerative conditions. The majority of these studies are case reports or small case series/cohort studies that may limit the conclusions that can be drawn about the clinical utility of SPECT.[1-41] Furthermore, evidence regarding the use of SPECT to evaluate brain function for a number of clinical indications listed above is limited to case series and studies that utilize SPECT as a component of the study design, but do not evaluate the clinical utility of this imaging technique compared to other standard modalities.

There have been comparative studies performed for a number of indications including autism, chronic fatigue syndrome, dementia, essential tremor, and stroke that were published more than ten years ago. However, these older studies are not described here.[3,42-54]

The evidence summarized below is focused on systematic reviews, randomized controlled trials, and comparative studies that investigate the utility of SPECT compared to other imaging modalities and/or standard clinical diagnostic criteria. In addition, the evidence summary only addresses the investigational indications listed in the policy criteria.

**CEREBROVASCULAR DISEASE**

**Nonrandomized Studies**

Kincaid et al. performed a retrospective analysis on 152 patients with subarachnoid hemorrhage to assess the accuracy of the routine clinical use of transcranial Doppler (TCD) ultrasonography and SPECT in predicting angiographically demonstrated cerebral vasospasm.[55] TCD was able to predict vasospasm with an odds ratio of 27 (95% confidence interval [CI] 3-243) in the anterior cerebral arteries (ACA), 17 (95% CI 5.4-55) in the middle cerebral arteries (MCA) and 4.4 (95% CI 0.72-27) in the basilar cerebral arteries (BA). Conversely, SPECT was able only to predict vasospasm with an odds ratio of 0.97 (95% CI 0.36-2.6) in the ACA, 2.0 (95% CI 0.71-5.5) in the MCA, and 5.6 (95% CI 0.89-36), in the BA. Overall, the investigators concluded that the standard transcranial Doppler appeared to be more predictive of cerebral vasospasms in multiple areas of the brain compared to SPECT.

**DEMENTIAS**
Archer et al. performed a Cochrane systematic review in 2015 to assess the diagnostic accuracy of cerebral blood flow (rCBF) SPECT for diagnosing frontal temporal dementia (FTD) in populations with suspected dementia settings and the ability of SPECT to differentiate between FTD from other dementia subtypes.\(^5\) Five cohort studies (two retrospective cohort studies and three prospective) were included to assess the diagnostic capabilities of SPECT in patients with suspected dementia.\(^5\) Six case-control studies were included that assessed the ability of SPECT to differentiate between different types of dementias in participants who had a clinical diagnosis of FTD or other dementia subtype using standard clinical diagnostic criteria.\(^5\) The review found that study design and methods varied widely between included studies, participant selection was not well described, and that the studies had either high or unclear risk of bias. The reviewers also reported that in most studies the threshold used to define a positive SPECT result was not predefined. Sensitivities and specificities for differentiating FTD from non-FTD ranged from 0.73 to 1.00 and from 0.80 to 1.00, respectively, for the three multiple-headed camera studies. However, sensitivities were significantly lower for the two single-headed camera studies; reporting sensitivities from 0.36 to 0.40. The reviewers recommended against the use of SPECT in these patients due to insufficient evidence.

In 2015, the Washington State Health Care Authority published a health technology assessment on “Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment.”\(^6\) This study assessed a number of neuroimaging techniques including FDG-PET, C-DTBZ-PET, SPECT and fMRI for the diagnosis of primary degenerative dementia or mild cognitive impairment. The authority concluded that there was sufficient evidence not to cover SPECT for these indications. The reliability of HMPAO-SPECT in providing a differential diagnosis of either AD or FTD in patients with an uncertain diagnosis was determined by the inclusion of two studies.\(^6\) The diagnostic accuracy of HMPAO-SPECT was determined by one study by Bonte et al., which found that SPECT had a sensitivity of 93% and a specificity of 85% in differentiating between AD and non-AD dementia in post-mortem samples.\(^6\)

Davison and O'Brien performed a systematic review in 2014 comparing FDG-PET and rCBF SPECT in the diagnosis of neurodegenerative dementias, including nine studies that directly compared the two imaging modalities (N=117 subjects with AD, 46 subjects with other dementias and 100 controls).\(^6\) Eight of these studies involved patients with AD, four of which included vascular dementia, frontal temporal dementia, or Pick's disease. One study examined patients with Dementia with Lewy Bodies.\(^4\) Published studies of SPECT sensitivities ranged from 65-85% for diagnosing Alzheimer's disease (AD) and specificities (for other neurodegenerative dementias) of 72-87%. PET sensitivities and specificities were slightly higher than SPECT, ranging from 75-99% and 71-93%, respectively. Both of these modalities are therefore just as sensitive at predicting and diagnosing AD as the current standard for clinical diagnosis, NINCDS-ADRDA, which has sensitivity ranging from 65-96%. Limitations of the included studies listed were small sample size, poorly matched control groups, and heterogeneity in study design.

Yeo et al. performed systematic review of the diagnostic utility of HMPAO SPECT in neurodegenerative dementia, and pooled studies with a clinical diagnosis and those using 99mTc-HMPAO SPECT in a meta-analysis.\(^6\) Forty-nine studies were included in the review; AD versus FTD (n = 13), AD versus VD (n = 18), AD versus DLB (n = 5), and AD versus NC (n = 18). However, the majority of these included studies had small sample sizes, with only 5
studies having more than 100 subjects. The reviewer reported sensitivity and specificity of 99mTc-HMPAO-SPECT in distinguishing clinically diagnosed AD from FTD are 79.7 and 79.9%, respectively, AD from VD are 74.5 and 72.4%, AD from DLB are 70.2 and 76.2%, and AD from NC are 76.1 and 85.4%. Limitations of this analysis include small numbers of studies for each diagnostic comparison group and high methodological heterogeneity between studies. The reviewers concluded that SPECT is valuable in differentiating Alzheimer’s disease from frontotemporal dementia and normal controls, but should only be used in with clinical information and other test results.

Nonrandomized Studies

Chiba (2016) evaluated the early differential diagnosis between Alzheimer’s disease and dementia with Lewy bodies which compared (18)F-FDG PET and (123)I-IMP SPECT.[66] The study was small with only nine patients limiting the conclusions that can be drawn. However, the authors concluded that for the occipital regions, there was significant accuracy in a differential diagnosis for both FDG PET and IMP SPECT. FDG PET was more useful than IMP SPECT for the differential diagnosis of mild cognitive impairment Alzheimer’s disease versus dementia with Lewy bodies.

O’Brien et al. compared the diagnostic ability of perfusion SPECT with FDG-PET to differentiate between Alzheimer and Lewy body dementias.[67] Subjects clinically diagnosed with Alzheimer disease (AD; n = 38) and dementia with Lewy bodies (DLB; n = 30), and controls (n = 30) underwent FDG-PET and SPECT; and area under the curve (AUC) of receiver-operating-characteristic analysis was reported. Investigators reported that diagnosis, as determined by two clinicians, indicated that FDG-PET was superior to SPECT for both dementia vs. no-dementia (AUC = 0.93 vs. 0.72, p=0.001) and AD vs. DLB (AUC = 0.80 vs. 0.58, p=0.005). The investigators concluded that perfusion SPECT is of limited diagnostic utility for differentiating DLB from AD.

Takahashi et al. compared the ability of perfusion SPECT with 3D arterial spin-labeled brain perfusion imaging to diagnose AD.[68] This study included 68 patients with clinically suspected AD who underwent both 3D arterial spin-labeling and SPECT. Images were assessed by two clinicians and the area under the ROC curve distinguishing AD from non-AD was 0.80-0.82 for SPECT alone and 0.69 for 3D ASL images alone. Statistical parametric mapping showed that the perisylvian and medial parieto-occipital perfusion in the arterial spin-labeled images was significantly higher than that in the SPECT images. The investigators concluded that diagnostic performance of 3D arterial spin-labeling and SPECT for Alzheimer disease was almost equivalent.

Ito et al. performed a multicenter prospective cohort study to examine the ability of 123I-N-isopropyl-4-iodoamphetamine cerebral blood flow (IMP-CBF) SPECT to diagnose AD in patients with mild cognitive impairment (MCI).[69] One hundred and thirteen patients with amnestic MCI underwent clinical and neuropsychological examinations and 123I-IMP-CBF SPECT at baseline and were followed for three years and evaluated for progression to dementia. SPECT images were classified as AD/DLB (dementia with Lewy bodies) pattern and non-AD/DLB pattern by image interpretation. Ninety-nine of the 113 patients converted to AD within the observation period. Image interpretation predicted conversion to AD with 56% diagnostic accuracy (sensitivity, 76%; specificity, 39%). Multivariate logistic regression analysis identified SPECT as a predictor, which distinguished AD converters from non-converters. The ability of a positive SPECT to predict conversion to AD on its own was low (odds ratio [OR] 2.5,
but if used in combination with gender and mini-mental state examination there was an improved diagnostic accuracy (OR 20.08). Therefore, SPECT on its own was concluded to be sensitive but relatively nonspecific for prediction of clinical outcome during the 3-year follow-up.

**MULTIPLE SCLEROSIS**

**Nonrandomized Studies**

Assadi et al. performed a small study of 16 patients with confirmed multiple sclerosis (MS) to evaluate with ability of SPECT with Tc-99m MIBI or Tc-99m ECD (ethyl cysteinate dimer) to detect brain abnormalities compared to MRI.[70] MRI was performed on 16 patients (13 women and 3 men, aged 16-38 years) and an average of 1-10 lesions in a number of different areas of the brain, including periventricular white matter, juxtacortical white matter, corpus callosum, cerebellar peduncles, and brainstem. Of the 16 patients, eight had SPECT with Tc-99m MIBI, and the other eight had SPECT with Tc-99m ECD. Neither type of SPECT was able to detect any abnormality, indicating that the use of SPECT is insufficient to evaluate brain lesions in multiple sclerosis.

**ESSENTIAL TREMOR**

**Systematic Reviews**

Sharifi et al. performed a systematic review of the role of neuroimaging techniques in the diagnosis and evaluation of essential tremor.[71] The reviewers included two small studies using SPECT to determine rCBF at rest.[72,73] One confirmed increased bilateral cerebellar activity, whereas the other did not find any significant differences between essential tremor patients and healthy controls. One study focused on cognitive functioning and related the rCBF with cognitive performances in patients and healthy controls, and determined differences in test performances, but showed no difference in rCBF values.[73]

**PARKINSONIAN SYNDROMES**

**Systematic Reviews**

In a 2007 systematic review of the literature on diagnostic accuracy of SPECT in parkinsonian syndromes, Vlaar et al. included 15 small case series that used SPECT with post-synaptic tracers, which measure dopamine receptor density.[42] When SPECT was used to differentiate between PD and essential tremor (ET), two studies were included and the pooled odds ratio with 95%CI was 2 (0.4–5). Five studies were included in a pooled analysis to determine if SPECT could reasonably differentiate between PD and atypical parkinsonian syndromes, with a pooled odds ratio pooled odds ratio with 95% CI of 2.0 (0.8 – 6). The reviewers concluded that the accuracy of SPECT with post-synaptic tracers to differentiate between PD and atypical parkinsonian syndrome is relatively low.

**PRACTICE GUIDELINE SUMMARY**

**AMERICAN PSYCHIATRIC ASSOCIATION (APA)**

An APA 2012 consensus report from the APA work group on neuroimaging markers of psychiatric disorders,[74] recommends the following steps for biomarker validation in psychiatric disorders:

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1. There should be at least two independent studies that specify the biomarker’s sensitivity, specificity, and positive and negative predictive values;
2. Sensitivity and specificity should be no less than 80%; positive predictive value should approach 90%;
3. The studies should be well powered, conducted by investigators with expertise to conduct such studies, and the results published in peer-reviewed journals;
4. The studies should specify type of control subjects, including normal subjects and those with a dementing illness but not AD; and
5. Once a marker is accepted, follow-up data should be collected and disseminated to monitor its accuracy and diagnostic value.

According to this standard, the report concludes, “...the psychiatric imaging literature currently does not support the application of a diagnostic biomarker to positively establish the presence of any primary psychiatric disorder.”

AMERICAN COLLEGE OF RADIOLOGY (ACR)

The 2015 ACR Appropriateness Criteria® for evaluating head trauma[75] indicated that SPECT is usually not appropriate (rating: 1) in the following situations:

- Initial evaluation of minor, mild, moderate or severe acute closed head injury
- Short-term follow-up imaging of acute traumatic brain injury with or without neurologic deterioration, delayed recovery, or persistent unexplained deficits
- Subacute or chronic traumatic brain injury with new cognitive and/or neurologic deficit(s)
- Suspected intracranial arterial injury
- Suspected intracranial venous injury

The 2014 Appropriateness Criteria® for evaluating seizures and epilepsy[76] indicated that SPECT with perfusion agents may be appropriate (rating: 5) to provide confirmatory localization information in patients with medically refractory epilepsy. However, the ACR guidelines conclude, "Only electroencephalogram (EEG) (using either scalp electrodes or intracranial electrodes [iEEG]) and magnetoencephalography (MEG) directly measure the brain's electrical activity. As such, they could or should be the gold standard for seizure localization.” In addition, the ACR guidelines state that the utility of SPECT with regards to clinical diagnosis, management, or outcomes of new-onset seizure patients has not been scientifically established.

The 2015 ACR Appropriateness Criteria® for dementia and movement disorders[77] provides guidance on the use of SPECT. A rating of 2 or 3 (“usually not appropriate”) was assigned to the following conditions:

- Dementia and movement disorders (consider for problem solving)
- Probable or possible Alzheimer’s disease
- Suspected frontotemporal dementia
- Suspected vascular dementia
- Suspected normal pressure hydrocephalus
- Suspected Huntington disease
- Clinical features suggestive of neurodegeneration with brain iron accumulation

July 1, 2017  Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
• Motor neuron disease (consider for problem solving)
• Parkinson disease with typical clinical features and responsive to levodopa
• Parkinsonian syndrome with atypical clinical features not responsive to levodopa.

A rating of 4 or 5 (“may be appropriate”) was assigned to the following conditions:
• Suspected prion disease (Creutzfeldt-Jakob, iatrogenic, or variant)
• Suspected dementia with Lewy bodies
• Parkinson disease with typical clinical features and responsive to levodopa.

The 2016 ACR-Society for Pediatric Radiology (SPR)[78] developed a practice parameter that states SPECT brain perfusion is clinically indicated for the following:
• Evaluating patients with suspected dementia
• Localizing epileptic foci preoperatively
• Diagnosing encephalitis
• Monitoring and assessing vascular spasm following subarachnoid hemorrhage
• Mapping of brain perfusion during interventions
• Detecting and evaluating cerebrovascular disease
• Predicting the prognosis of patients with cerebrovascular accidents
• Corroborating the clinical impression of brain death

In addition, for other indications, such as neuropsychiatric disorders and chronic fatigue syndrome, the findings of SPECT brain perfusion imaging have not been fully characterized. In human immunodeficiency virus (HIV) encephalopathy, SPECT brain perfusion imaging can detect altered brain perfusion.

### SUMMARY

There is not enough research to show that single photon emission computed tomography (SPECT) of the brain in the evaluation, diagnosis or treatment for a variety of indications improves health outcomes. Additional research is needed to know how SPECT may be used to guide patient management compared to other imaging techniques and standard clinical diagnostic criteria. Therefore, SPECT of the brain is considered investigational for the neurologic, psychiatric, psychological, as well as other nononcologic indications as specified in the policy criteria. All other uses for SPECT of the brain have shown in the research to improve health outcomes and may be considered medically necessary.

### REFERENCES


48. Schmidt, D, Zimmermann, R, Lewczuk, P, et al. Confirmation rate of blinded (99m)Tc-SPECT compared to neurochemical dementia biomarkers in CSF in patients with


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<th>Codes</th>
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_Date of Origin: March 2005_
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Medical Policy Manual

**Topic:** Virtual Colonoscopy/CT Colonography

**Section:** Radiology

**Policy No:** 36

**Date of Origin:** October 2001

**Last Reviewed Date:** July 2016

**Effective Date:** August 1, 2016

**IMPORTANT REMINDER**

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**DESCRIPTION**

Computed tomography colonography (CTC), also known as “virtual colonoscopy,” is an imaging modality that uses thin-section helical CT to generate high-resolution 2-dimensional images of the colon. From these images, three-dimensional pictures may then be reconstructed which resemble the images obtained with conventional endoscopic (“optical”) colonoscopy.

Diseases of the colon and rectum for which CT colonography may be considered as a diagnostic or screening tool include colorectal cancer and precancerous conditions, diverticulosis and diverticulitis, and inflammatory bowel disease. However, CTC has been primarily investigated as an alternative screening technique to colonoscopy for colorectal cancer (CRC). While CTC requires a full bowel preparation, similar to conventional colonoscopy, no sedation is required. However, the technique involves gas insufflation of the intestine, which may be uncomfortable to the patient.

**MEDICAL POLICY CRITERIA**

I. Computed tomography (CT) colonography may be considered **medically necessary** for patients who meet one of the following criteria:
A. A conventional colonoscopy is indicated but the patient is unable to undergo conventional colonoscopy for medical reasons (e.g., continuous anticoagulation therapy or high anesthesia risk); or

B. Conventional colonoscopy was incomplete because of colonic stenosis, obstruction, or significant anatomical abnormality.

II. Except as noted in the criteria above, CT colonography is considered not medically necessary.

SCIENTIFIC EVIDENCE[1]

Conventional endoscopic colonoscopy is the standard of care diagnostic and screening technique for colon cancer and other gastrointestinal disorders, such as diverticulitis and ulcerative colitis. Suspicious lesions of any size can be removed immediately and evaluated for the presence of colorectal cancer (CRC) or dysplasia.[2-4]

In order to demonstrate its efficacy, computed tomography colonography (CTC) needs to be compared to the standard of care, conventional colonoscopy, in randomized controlled trials.

Literature Appraisal

Technology Assessment

A 2009 BlueCross and BlueShield Association (BCBSA) Technology Evaluation Center (TEC) Assessment evaluated the scientific literature comparing the effectiveness of CTC to that of conventional colonoscopy.[4] This assessment concluded:

Based primarily on the results from 2 large trials in asymptomatic patient populations,[5,6] CTC sensitivity for the detection of lesions 10 mm or larger approaches the sensitivity of conventional colonoscopy.

However, the diagnostic performance of CTC was highly dependent on the technology and techniques used. If these practices (e.g., use of the most current CT scanners, stool tagging techniques, and highly trained radiologists) can be replicated in the community, then it is likely that improved health outcomes can be achieved outside the investigational setting.

Systematic Reviews

In 2014, Plumb et al. published findings from a systematic review and meta-analysis of studies evaluating the performance of CT colonography for the diagnosis of colon cancer among subjects with positive fecal occult blood test (FOBT).[7] FOBT is a recommended screening technique for colorectal cancer; positive tests are typically followed up with colonoscopy. In this meta-analysis, the authors included only studies that used CT colonography in the evaluation of patients who had had a positive FOBT and compared colonography results to a reference test; either conventional colonoscopy, segmental unblinded colonoscopy, or surgery with subsequent histopathology. Five articles were included in the authors’ analysis, representing 622 patients. Pooled per-patient sensitivity and specificity
for adenomas greater than or equal to 6 mm or colorectal cancer were 88.8% (95% CI 83.6% to 92.5%) and 75.4% (95% CI 58.6% to 86.8%), respectively.

Two meta-analyses were reported in 2011. One analysis of five studies with a total of 4,086 participants reported that CT colonography has a high sensitivity for adenomas ≥10mm, but lower sensitivity for adenomas ≥6mm.[8] The other included 49 studies (N=11,151 patients); the sensitivity of CT colonography for CRC was 96.1% (95% CI, 93.8 to 97.7%).[9]

The Centers for Medicare and Medicaid Services published an evidence-based decision memo (2009) that stated, “The evidence is inadequate to conclude that CT colonography is an appropriate colorectal cancer screening test…”[2] This review noted the following uncertainties:

“CT colonography using at least 8 to 16 slice CT scanners has sensitivity and specificity that are comparable to optical colonoscopy for polyps ≥ 10mm. For polyps 6-9mm, the evidence is suggestive but less convincing given the lower sensitivity and specificity. CT colonography does not appear to have the ability to reliably detect small polyps < 6mm.

Since CT colonography cannot reliably detect polyps < 6mm, the impact of these polyps in the intervening screening interval is important but unknown at this point…Further research on the natural history of polyps < 6mm and nonpolypoid lesions and their health outcomes is needed.

The value of an intermediate screening test such as CT colonography that does not have therapeutic options may well be reduced or negated if there is a high rate of referral to optical colonoscopy leading to duplicative tests.

Since extracolonic findings are common, evidence based standards and guidelines on reporting, monitoring and subsequent evaluation of these findings are needed…Since individuals undergoing screening are asymptomatic by definition, the potential impact of extracolonic findings on health outcomes needs to be determined prior to general use of this modality.”

The 2008 Agency for Healthcare Research and Quality (AHRQ) systematic review of tests used for colorectal cancer screening concluded the following with regard to CTC technology:[10]

The published reports on CTC screening suggested at least comparable sensitivity to colonoscopy for CRC and large adenomas (10mm or larger).

For smaller polyps (6mm or larger), published data were inconsistent, with some studies suggesting either reduced sensitivity or sensitivity that may be dependent upon the CT technology used and the expertise of the individual reader.

Published specificity estimates for CTC were consistently high for large polyps (>96%), but appeared lower and more variable (80-94%) for smaller polyps (6mm or larger). Approximately 40% of patients had extracolonic findings; however, the net impact of these findings was uncertain in terms of added benefits or harms.

A 2011 meta-analysis of CTC diagnostic performance included 33 prospective studies in 6,393 adult patients.[11] Heterogeneity was addressed through statistical analysis and by performing stratified analyses of confounding variables. This study reported that the sensitivity of CTC varied, but improved as polyp size increased:
Sensitivities ranged from 48% for detection of polyps smaller than 6 mm, to 70% for polyps 6 to 9 mm, to 85% for polyps larger than 9 mm.

In contrast, specificity was more consistent (92% for polyps smaller than 6 mm, 93% for polyps 6 to 9 mm, and 97% for polyps larger than 9 mm).

In a subanalysis, characteristics of the CT scanner technology explained only some of the variation between studies.

**Randomized Controlled Trial (RCT)**

In 2013, Atkin et al. reported results from an RCT comparing colonoscopy and CT colonography in the evaluation of patients with symptoms suggestive of colorectal cancer. The study randomly allocated patients aged 55 or older with symptoms suggestive of colorectal cancer in a 2:1 fashion to either colonoscopy or CT colonography. The study was not blinded. Both colonoscopy and CT colonography procedures were conducted with a full bowel preparation. The study’s primary outcome was the proportion of patients who had additional colonic investigation, defined as any subsequent examination of the colon until diagnosis (usually histological confirmation of a cancer or polyp) or until a patient was referred back to his or her family doctor. Additional diagnostic evaluation of the colon was required in 160/533 (30.0%) of those assigned to CT colonography, compared to 86/1047 (8.2%) of those assigned to colonoscopy (p<0.0001). The overall detection rate for colorectal cancer or large polyps did not differ between the groups (relative risk [RR] 0.95; 95% CI 0.70 to 1.27; p=0.69). The authors concluded that the high referral rate for additional procedures could potentially be mitigated with wider implementation of CT colonography, radiologist training, and standardized protocols.

**Nonrandomized Studies**

In 2014, Fini et al. reported results from a study on the diagnostic accuracy of CT colonography for clinically relevant colorectal lesions, defined as polyps or masses greater than or equal to 6 mm among first degree relatives of patients with colorectal cancer. CT colonography was undertaken following a non-cathartic bowel preparation among 344 patients, with optical colonoscopy undertaken on the following day. Sensitivity and specificity for lesions greater than or equal to 6 mm were 77% (95% confidence interval [CI] 59% to 95%) and 99% (95% CI 97% to 100%), respectively.

The diagnostic accuracy of CT colonography compared to colonoscopy was recently assessed in a study by Zalis et al. in 2012. A laxative-free bowel preparation technique for CT colonography was used in 605 patients aged 50 to 85 years with average to moderate colon cancer risk. Sensitivity and specificity were calculated on a per-patient basis and authors reported that for adenomas 10mm or larger 91% (95% confidence interval [CI] 71% to 99%) and 85% (95% CI 82% to 88%), respectively. The sensitivity of CT colonography was similar but slightly lower than colonoscopy. For smaller adenomas, the sensitivity of CT colonography was lower than colonoscopy.

The remaining evidence on CTC diagnostic performance is not reliable for one or more of the following reasons:

- High-risk subjects were included (e.g., symptomatic patients, patients referred for additional testing, or those with a family history of cancer). These subjects are not representative of a screening population and may create selection bias.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Study populations sizes were too small, which limits the ability to rule out the role of chance as an explanation of findings and does not permit conclusions for a test that is intended to be used in a large screening population.\cite{4,15,21}

Estimates of sensitivity were based on a per polyp (rather than per patient) basis. These estimates may result in misleading calculations of sensitivity, and they do not reflect how the test would be used in the clinical setting.\cite{4,15}

Older CTC machinery or screening techniques were used, which is not reflective of the current technology. These studies may not accurately reflect the best diagnostic performance of CTC.\cite{4} In addition, variability in performance of older scanners or imaging techniques limits comparisons between studies and may introduce performance bias.

CTC and conventional colonoscopy were compared in separate patient populations. These studies do not allow calculation of sensitivity and specificity between the two tests in the same patient population and only give an estimate of the diagnostic yield of each test.\cite{4,22,23}

Cost-effectiveness

In 2012, Hanly and colleagues published a systematic review of cost-effectiveness studies of CT colonography and concluded that CT colonography is cost-effective compared to no screening.\cite{24} They could not reach a conclusion regarding a comparison to colonoscopy, due to differences in study parameters and assumptions. It was noted that early studies demonstrated that colonoscopy was both more effective and less expensive than CTC; however, more recent studies have had variable results, dependent on the threshold for colonoscopy referral and whether the costs and effects of acting upon extra-colonic findings seen on CT colonography are addressed.

A 2009 BCSBA TEC Special Report evaluated 7 studies appraising the cost-effectiveness of CTC compared with conventional colonoscopy. This report determined that in general, conventional colonoscopy was the more effective screening test. CTC was generally more expensive and in many analyses less effective as a screening strategy than colonoscopy.\cite{25} Subsequent to the BCBSA TEC Report, several cost-effectiveness analyses of colon cancer screening techniques also reported that CT colonography is not cost-effective compared with the established screening options.\cite{26,27}

Clinical Practice Guidelines

Much of the evidence supporting colorectal cancer screening is indirect and consensus groups reviewing the same evidence have come to differing conclusions regarding the evidence on CTC for colon cancer screening.\cite{4,28}

Evidence-based Guidelines

U.S. Preventive Services Task Force

The 2016 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for colorectal cancer determined the evidence was insufficient to evaluate the potential harms of extracolonic findings, which are common, when performing CT colonography.\cite{29} CTC can result in overdiagnosis and overtreatment following extracolonic findings, which occur in 40 to 70 percent of screening examinations. Since the 2008 USPSTF review, seven new studies examined the potential harms of CTC, though the findings were inconsistent.

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harm associated with CT colonography, however high quality evidence from which conclusions can be drawn remains lacking. The USPSTF found no studies demonstrating any screening method was more effective than others.

Consensus-based Guidelines

While these guidelines report outcomes of numerous studies, the authors did not provide a critical analysis of the quality of the studies, and/or did not rate the strength of the evidence supporting their recommendations:

A 2012 American College of Physicians (ACP) position statement for colorectal cancer screening indicated the ACP, “recommends using a stool-based test, flexible sigmoidoscopy, or optical colonoscopy as a screening test in patients who are at average risk. ACP recommends using optical colonoscopy as a screening test in patients who are at high risk.”[30]

In 2012, the American College of Gastroenterology, along with the American Gastroenterological Association Institute and the American Society for Gastrointestinal Endoscopy, updated the 2006 guidelines on colonoscopy surveillance after polypectomy.[31] This guideline makes the following statement on CT colonography and other newer colonic imaging technologies: “The role of new endoscopic technologies has not been studied in surveillance cohorts, although there are ongoing studies of CT colonography.... At this point, these technologies technology do not have an impact on surveillance intervals.”

The 2009 American College of Gastroenterology Guidelines for colorectal cancer screening recommended colonoscopy every 10 years, beginning at age 50, as the preferred CRC screening strategy. However, these guidelines note that not all eligible persons are willing to undergo colonoscopy for screening purposes and recommend, in these cases, patients be offered an alternative CRC prevention test such as flexible sigmoidoscopy every 5 to 10 years, CTC every 5 years, or a cancer detection test such as fecal immunochemical test for blood.[3]

A 2008 joint position statement issued by the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology stated colon cancer prevention is the primary goal of colorectal cancer screening and endorsed CT colonography every 5 years as one screening option.[32,33]

The 2007 AGA Standards for Gastroenterologists Performing and Interpreting Diagnostic CTC stated, “Based on currently available data, CT colonography is not endorsed as a primary screening modality for CRC in asymptomatic adults.”[34]

A 2006 American Gastroenterological Association (AGA) position paper stated that peer-reviewed published data suggest that CT colonography is only indicated as a diagnostic tool for patients who have undergone incomplete colonoscopies for limited indications.[35]

The 2006 American Society for Gastrointestinal Endoscopy stated, “Virtual colonoscopy is an evolving technique and is not currently recommended as the primary method of screening for CRC.”[36]
A number of questions remain unanswered in the published scientific literature with respect to the safety of CTC:

The lifetime cumulative radiation risk from use of CTC in addition to other medical diagnostic or screening tests is uncertain and needs further evaluation.[2,4,29]

The best interval for repeat CTC after negative CT colonography is unknown and needs to be established.[2,3,6] Insufficient follow-up may lead to under treatment and too frequent follow-up may lead to unnecessary radiation exposure.

The natural history of smaller adenomas, particularly those of different sizes (e.g. < 10mm) is unknown.[29] It is not clear that leaving small polyps is safe; there are no long-term, adequately controlled studies on the subject.[2,4,6,10,15]

How to interpret and manage additional CT findings outside the colon (extracolonic findings) is not well defined.[2,4,5,10,15] False positive findings may lead to unnecessary procedures. Interdisciplinary algorithms for management of these findings are needed.[5,29]

Summary

Computed tomography colonography (CTC) has not been shown to be superior to colonoscopy as a screen for colorectal cancer or to diagnose other gastrointestinal disorders, such as diverticulitis and ulcerative colitis. Evidence suggests CTC is as sensitive as conventional colonoscopy for detecting lesions 10 mm or larger. However, for lesions less than 10 mm, the evidence is inconsistent and suggests CTC is less sensitive. If suspicious lesions are found on CTC, they cannot be immediately removed and evaluated. Patients must be referred for conventional colonoscopy for lesion removal. Therefore, except in patients who are unable to undergo conventional colonoscopy for medical reasons or for whom conventional colonoscopy was incomplete because of colonic stenosis, obstruction, or significant anatomical abnormality, CT colonography is considered not medically necessary.

REFERENCES

1. BlueCross BlueShield Association Medical Policy Reference Manual "Virtual Colonoscopy/CT Colonography." Policy No. 6.01.32


CROSS REFERENCES
Computed Tomography to Detect Coronary Artery Calcifications, Radiology, Policy No. 06 http://blue.regence.com/trgmedpol/radiology/rad06.pdf
Whole Body CT Screening, Radiology, Policy No. 40 http://blue.regence.com/trgmedpol/radiology/rad40.pdf
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