Uniform Medical Plan coverage limits

Updates effective 11/1/2018

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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- C9747, 0398T
- UMP is subject to HTCC decision: 78607
- Functional neuroimaging for primary degenerative dementia or mild cognitive impairment is not a covered benefit for 78607

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.
Radiology Quality Initiative

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

We partner with AIM to administer our Radiology Quality Initiative (RQI) program.

- Phone 1 (877) 291-0509
Contact AIM to obtain an order number for the following codes:

70336, 70450, 70460, 70470, 70480, 70481, 70482, 70486, 70487, 70488, 70490, 70491, 70492, 70496, 70498, 70540, 70542, 70543, 70544, 70545, 70546, 70547, 70548, 70549, 70551, 70552, 70553, 70554*, 70555*, 71250, 71260, 71270, 71275, 71550, 71551, 71552, 71555, 72125, 72126, 72127, 72128, 72129, 72130, 72131, 72132, 72133, 72141, 72142, 72146, 72147, 72148, 72149, 72150, 72151, 72156, 72157, 72158, 72159, 72191, 72192, 72193, 72194, 72195, 72196, 72197, 72198, 73200, 73201, 73202, 73206, 73218, 73219, 73220, 73221, 73222, 73223, 73225, 73700, 73701, 73702, 73706, 73718, 73719, 73720, 73721, 73722, 73723, 73725, 74150, 74150, 74170, 74174, 74175, 74176, 74177, 74178, 74181, 74182, 74183, 74185, 74712, 75557, 75559, 75561, 75563, 75572, 75573, 75574, 75635, 77058, 77059, 77078, 77084, 78451, 78452, 78453, 78454, 78459, 78460, 78468, 78469, 78472, 78473, 78481, 78483, 78491, 78492, 78494, 78608*, 78609, 78811, 78812, 78813, 78814, 78815, 78816, 93303, 93304, 93306, 93307, 93308, 93312, 93313, 93314, 93315, 93316, 93317, 93350, 93351

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*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 (DAT-SPECT)

Effective: March 1, 2018

Next Review: January 2019
Last Review: January 2018

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. Magnetic Resonance Spectroscopy, Radiology, Policy No. 27
2. Single Photon Emission Computed Tomography (SPECT) for the Diagnosis of ADHD, Dementias and Other Psychiatric Conditions, Radiology, Policy No. 44
3. Biochemical Markers of Alzheimer's Disease, Laboratory, Policy No. 22
4. Deep Brain Stimulation, Surgery, Policy No. 84
5. 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 \(^{123}\text{I}-\beta\text{-CIT}\), \(^{123}\text{I}-\text{FP-CIT}\), and \(99\text{mTc-TRODAT-1}\). \(^{123}\text{I}-\beta\text{-CIT}\) requires a delay between injection and scan of about 24 hours. \(^{123}\text{I}-\text{FP-CIT}\) (DaTscan™) is a fluoropropyl derivate of \(\beta\text{-CIT}\) 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.\(^5\) \(^{123}\)I-β-CIT is a cocaine analog that has a high affinity to the DAT and serotonin transporters. \(^{123}\)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 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.

In a 2012 study, Papathanasiou 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 reported a prospective study on the diagnostic accuracy of visual assessment of DAT-SPECT in individuals with early-stage parkinsonian diseases. 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 one 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 two 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, 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). 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 (κ 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 reported a meta-analysis of DAT-SPECT to differentiate between PD and vascular or drug-induced parkinsonisms. 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 (2012) The studies included 92 patients with clinically uncertain parkinsonian syndromes (CUPS) at baseline who had confirmed clinical diagnosis at one year. Bajaj (2014) assessed the effect of age, disease stage, and other clinical and neurocognitive measures on the diagnostic performance of DAT-SPECT. Hauser (2014) reported that the diagnostic accuracy of DAT-SPECT was higher than clinical diagnosis at baseline. 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 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). 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 four 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 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 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 (2014) 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.[17] 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 (2014) reported a retrospective study of the diagnostic accuracy of PD by general neurologists.[18] 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.

One study addressed the use of DAT-SPECT in asymptomatic LRRK2 G2019S carriers for predicting conversion to PD.[19] In this prospective study by Sierra (2017), 32 asymptomatic carriers of LRRK2 G2019S were evaluated at baseline and four years later, including clinical examination and DAT-SPECT. Three carriers had converted to PD at the second evaluation, and these participants had a statistically significantly lower striatal DAT binding at baseline than those that did not convert. There was no significant difference between the slope of DAT binding decline between the two scans.

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.
Bhattacharjee (2017) retrospectively assessed the impact of DAT-SPECT performed for diagnosis and clinical management.[20] Of a total of 48 scans reported, 24 were to confirm early Parkinson’s disease, five were to exclude drug-induced parkinsonism, eight were to distinguish essential tremor from parkinsonism, two were to distinguish Lewy body diseases from Alzheimer’s dementia, and four were for other indications. There were 26 abnormal scans and 21 scans confirmed a diagnosis of degenerative parkinsonism. In 23% of patients, the scan results altered diagnosis and management.

Oravivattanakul (2015) reported on the concordance between pre-scan diagnosis and scan results in 175 CUPS patients who were seen by movement disorders neurologists.[21] 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 (2015) also reported on the clinical outcome of the change in management.[22] 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.

In a retrospective study from a hospital imaging facility in Europe, Thiriez (2015) evaluated whether routine clinical requests for DAT-SPECT were considered appropriate or inappropriate and whether the results led to a change in management.[23] Appropriateness was determined by consensus of two 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).

Bega (2015) reported a study from a tertiary care center that evaluated 83 scans ordered over a two-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 (2013) found that confidence in a diagnosis of PD or non-PD was significantly increased with abnormal scans, but not with normal scans.[25] For many patients, the scan confirmed the diagnosis of PD, despite a poor response to medication and resulted in a change in medication.
In 2012-2013, Kupsch reported an industry-sponsored, open-label, multicenter randomized trial from 19 university hospital centers in Europe and the United States that assessed the impact of DAT-SPECT on diagnosis, confidence of diagnosis, clinical management, health resource use, and safety in 273 patients with CUPS.[11,26] 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 four weeks, 12 weeks, one year) by neurologists with (n=12) or without (n=7) movement disorder specialization.

The primary outcome was the proportion of patients in the efficacy population (baseline and 12-week visits) who had one or more changes in clinical management. Significantly more patients in the DAT-SPECT group had at least one change in their clinical management plan by 12 weeks than the control group (50% vs 31%, p=0.002). This was due to a greater change in management by movement disorder specialists (51% DAT-SPECT vs 28% controls, p<0.001). Medications were initiated in 29% of patients and withdrawn in 18% of patients after DAT-SPECT (patients could be counted in both categories). Changes included initiation of dopaminergic therapy or more aggressive dopaminergic therapy in patients with an abnormal scan, discontinuation of dopaminergic therapy, or initiation of tremor control drugs in patients with a normal scan, and unplanned diagnostic tests. For the general neurologists, clinical management was not affected by the DAT-SPECT results, with a change in management in 48% of DAT-SPECT patients versus 43% of controls. Changes in diagnosis occurred in 45%, 46%, and 54% of DAT-SPECT patients by four weeks, 12 weeks, and one year, respectively (per protocol population), compared with a change in diagnosis in 9%, 12%, and 23% of control patients at the same time points (p<0.001 for all comparisons). The changes were in the direction of better agreement between the clinical diagnosis and imaging results. Clinicians had increased confidence in diagnosis at four weeks, 12 weeks, and one 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 one-year follow-up period. No serious adverse events occurred during the study.

Bairactaris evaluated the impact of DAT-SPECT on diagnoses of patients with PS in a 2009 report.[27] 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 one-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 two-year follow-up reported in 2007. 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 reclassified and 16 of 118 patients (14%) were reclassified as inconclusive. Overall, imaging resulted in a change in the diagnosis in 52% of patients and in a change in management in 72% of cases. All patients with a final diagnosis of presynaptic PS had an abnormal image, whereas 94% of patients with nonpresynaptic PS had a normal scan.

At two years, 85 patients (72%) were available for follow-up. 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.

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.

**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 (e.g.,
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 one-year follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

DEMENTIA WITH LEWY BODIES

Clinical Validity

In a 2017 study by Shimizu, DAT-SPECT was performed in 95 AD patients and 133 DLB patients and the relationship between symptoms and DAT uptake was examined.\[33\] Patients with parkinsonism had significantly lower DAT uptake than AD patients in the entire striatum, entire putamen, and anterior putamen but there were no differences in any subregion of the striatum. There was a small but statistically significant correlation between severity of parkinsonism and DAT uptake in the entire striatum in patients with DBL. Other symptoms examined did not correlate with DAT uptake in any region of the striatum.

A 2015 meta-analysis by Brigo evaluated the diagnostic accuracy of DAT-SPECT to distinguish between DLB and other dementias.\[34\] 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 reported a meta-analysis of the diagnostic accuracy of DAT-SPECT in DLB in 2012.\[35\] Four studies with a total of 419 patients were included in the meta-analysis (including the study by McKeith 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, who assessed 326 patients with clinical diagnosis of probable (n=94) or possible (n=57) DLB or non-DLB (n=147).\[36\] 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 (2016) reported on seven (10.4%) of 67 patients who were clinically diagnosed with DLB but had normal scans.[37] 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 reported a longitudinal study of patients who had inconsistent clinical criteria for DLB and DAT-SPECT results at baseline.[38] Fifty patients were evaluated with clinical criteria and DAT-SPECT results and followed for two to five 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 seven 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 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.[39] 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 (e.g., 71% revised vs 16%, p<0.001) and were more confident in their diagnosis (p<0.001). Clinicians were also more likely to change the diagnosis if the scan was abnormal than if it was normal (82% vs 46%).

Kemp (2011) conducted a retrospective study of the impact of DAT-SPECT on the clinical diagnosis and subsequent management of 80 consecutive patients with possible DLB.[40] 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.[41] 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; five class III studies).[42] 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.[43] 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.[4] 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 (e.g., 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 dopamine transporter single-photon emission computed tomography (DAT-SPECT) is considered investigational for all indications.

**REFERENCES**


41. ACR Appropriateness Criteria®: Dementia and Movement Disorders. [cited 1/20/2017]; Available from: https://acsearch.acr.org/docs/69360/Narrative/


44. BlueCross BlueShield Association Medical Policy Reference Manual "Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography." Policy No. 6.01.54

**CODES**

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<thead>
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<th>Codes</th>
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*Date of Origin: January 2016*
Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation

Effective: September 1, 2018

Next Review: August 2019
Last Review: August 2018

DESCRIPTION

Magnetic resonance (MR) guided focused ultrasound (MRgFUS) and high intensity focused ultrasound (HIFU) concentrate high-energy ultrasound waves via probe on a single location to cause coagulative necrosis.

MEDICAL POLICY CRITERIA

I. High-intensity focused ultrasound (HIFU) may be considered medically necessary as a local treatment for prostate cancer when all of the following (A.-D.) criteria are met:
   A. For the treatment of radiation recurrence (see Policy Guidelines); and
   B. The patient is a candidate for local therapy (see Policy Guidelines); and
   C. Transrectal ultrasound guided (TRUS) biopsy positive; and
   D. In the absence of metastatic disease.
II. HIFU is considered **investigational** for all other indications not meeting policy criteria, above.

III. Magnetic resonance (MR) guided focused ultrasound (MRgFUS) may be considered **medically necessary** for medicine-refractory essential tremors.

IV. Magnetic resonance (MR) guided focused ultrasound (MRgFUS) is considered **investigational** for all indications, including but not limited to treatment of the following:
   A. Uterine fibroids
   B. All tumors, including but not limited to brain, breast, prostate and renal
   C. Bone metastases for palliation of pain

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

### POLICY GUIDELINES

#### REQUIRED DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical
- Treatment plan including treatment area
- For essential tremors, clinical documentation must demonstrate medicine-refractory symptoms
- For prostate cancer treatment, clinical documentation must also demonstrate results from transrectal ultrasound guided (TRUS) biopsy

#### CANDIDATE FOR LOCAL THERAPY

According to National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 3.2018), in the presence of radiation therapy recurrence (see below), a candidate for local therapy includes:

- Original clinical stage T1-T2, NX or N0
- Life expectancy > 10y
- PSA now < 10 ng/mL

#### RADIATION RECURRENCE

NCCN guidelines for prostate cancer (version 3.2018) cite radiation therapy recurrence as either 1) a positive digital rectal exam (DRE), or 2) Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology (RTOG-ASTRO) Phoenix Consensus biochemical failure.

RTOG-ASTRO Phoenix Consensus biochemical failure is further defined as:

1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and
2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy.

Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

CROSS REFERENCES

1. Radioembolization for Primary and Metastatic Tumors of the Liver, Medicine, Policy No. 140
2. Radiofrequency Ablation of Tumors (RFA), Surgery, Policy No. 92
3. Cryosurgical Ablation of Miscellaneous Solid Tumors, Surgery, Policy No. 132
4. Microwave Tumor Ablation, Surgery, Policy No. 189
5. Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204

BACKGROUND

Magnetic resonance (MR) guided focused ultrasound (MRgFUS) and high intensity focused ultrasound (HIFU) are proposed as less invasive approaches than surgery for treatment of localized prostate cancer, uterine fibroids, and pain palliation of bone metastases. Broadly, these devices use an integrated imaging system to take measurements, confirm the treatment area, and monitor thermal destruction in real time.

MRgFUS is a noninvasive treatment that combines focused ultrasound and magnetic resonance imaging (MRI). The ultrasound beam penetrates through the soft tissues and, using MRI for guidance and monitoring, the beam can be focused on targeted sites. Ultrasound causes a local increase in temperature in the target tissue, resulting in coagulation necrosis while sparing the surrounding normal structures. Ultrasound waves from each sonication are focused at a focal point that has a maximum focal volume of 20 nm in diameter and 15 nm in height/length. This causes a rapid rise in temperature (to approximately 65°C-85°C), which is sufficient to achieve tissue ablation at the focal point. In addition to providing guidance, the associated MRI can provide online thermometric imaging that provides a temperature “map” to confirm the therapeutic effect of the ablation treatment and allow for real-time adjustment of the treatment parameters.

HIFU focuses high-energy ultrasound waves on a single location, which increase the local tissue temperature to over 80°C. This causes a discrete locus of coagulative necrosis of approximately 3×3×10 mm. In the treatment of prostate cancer, HIFU is a minimally invasive localized option. The surgeon uses a transrectal probe to plan, carry out, and monitor ablative treatment in a real-time sequence with a combination of ultrasound and MRI imaging.

REGULATORY STATUS

Devices have received U.S. Food and Drug Administration (FDA) approval via the De Novo and Premarket Application (PMA) processes:

HIFU

The Sonablate® 450 (SonaCare Medical) is the first high intensity ultrasound system for prostate tissue ablation to receive FDA approval, and therefore underwent the de novo
application process, obtaining clearance in 2015. Shortly thereafter, Ablatherm Integrated Imaging® (EDAP TMS) received PMA approval.

**MRgFUS**

MRgFUS systems may also be referred to as “high intensity” ultrasound.

The ExAblate® 2000 System (InSightec, Inc.) was approved for two indications: “ablation of uterine fibroid tissue in pre- or peri-menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure,” and for palliation of pain associated with tumors metastatic to bone.[1]

For uterine fibroids, the FDA approval letter states that patients must have a uterine gestational size of less than 24 weeks and those patients must have completed childbearing.

In the initial safety and efficacy studies, the FDA limited MRI-guided focused ultrasound to 33% of fibroid volume with a maximum treatment time of 120 minutes. Guidelines were later modified to allow up to 50% treatment volume, 180-minute maximum treatment time, and a second treatment if within a 14-day period.

The ExAblate 2000 treatment is contraindicated for use in women who have MRI-related issues, such as metallic implants, or sensitivity to MRI contrast agents; obstructions in the treatment beam path, such as a scar, skin fold, or irregularity, bowel, pubic bone, intrauterine device, surgical slips, or any hard implants; and fibroids that are close to sensitive organs such as the bowel or bladder, or are outside the image area.

The ExAblate® 2100 System also received approval through the PMA process.[2] It includes several modifications to the previous system including enhanced sonication and a detachable cradle, and only certain cradle types can be used for palliation of pain associated with metastatic bone cancer. Approval remains limited to treatment of patients with metastatic bone cancer who failed or are not candidates for radiation therapy; or, in patients with symptomatic uterine fibroids with a uterine size of less than 24 weeks and those who have completed childbearing.

In October 2012, the FDA approved the ExAblate® System, Model 2000/2100/2100 VI for pain palliation via the PMA process.[1] For pain palliation, the intended use of the device is in adult patients with metastatic bone cancer who failed or are not candidates for radiation therapy. The device was evaluated through an expedited review process. The FDA required a post-approval study with 70 patients to evaluate the effectiveness of the system under actual clinical conditions.

For treating pain associated with bone metastases, the aim of MRgFUS treatment is to destroy nerves in the bone surface surrounding the tumor. Metastatic bone disease is one of the most common causes of cancer pain. Existing treatments include conservative measures (e.g., massage, exercise), pharmacologic agents (e.g., analgesics, bisphosphates, corticosteroids) and radiotherapy, especially conventional external beam radiotherapy (EBRT) for tumors that do not involve the nervous system.

MRgFUS is also being studied for the treatment of other tumors, including breast, prostate, renal, and for brain tumors. However, the FDA has only approved MRI-guided ultrasound ablation devices for the treatment of uterine fibroids and for the treatment of tumors metastatic to bone for the palliation of pain.
HIGH INTENSITY FOCUSED ULTRASOUND (HIFU)

Prostate Cancer

Given significant uncertainty in predicting the behavior of individual localized prostate cancers, and the substantial adverse effects associated with definitive treatments, investigators have sought a therapeutic middle ground. The latter seeks to minimize morbidity associated with radical treatment in those who may not actually require surgery while reducing tumor burden to an extent that reduces the chances for rapid progression to incurability. Locally directed therapies, also termed focal treatment includes several ablative methods, one of which is high intensity focused ultrasound (HIFU). The overall goal of any focal treatment is to minimize the risk of tumor progression and preserve erectile, urinary, and rectal functions by reducing damage to the neurovascular bundles, external sphincter, bladder neck, and rectum.

As a salvage treatment, that is, for recurrent disease following initial therapy, Crouzet (2017) reported that HIFU is associated with cancer-specific (CSS) and metastasis-free survival (MFS) of at least 80% at 7-years in a study of over 400 men. Morbidity rate for grade III/IVa complications was 3.6%. Smaller studies with shorter-duration of follow-up are in general agreement, however, patient selection criteria is an important predictor of treatment outcomes. While this is still an area of investigation, there may be limited treatment for this population of men with recurrent disease. Current practice guidelines based on research recommend HIFU in the presence of radiation recurrence for carefully selected patients (e.g., no metastases, and good candidate for local therapy).

As a primary treatment, evidence for HIFU is still accumulating. Data in the published literature are available for shorter follow-up times than in salvage treatment studies (e.g., two years). Treatment free survival rate has been reported as 89% at two years, with acceptable morbidity – a grade III complication rate of 13%. Larger, longer-term comparative studies are needed.

MAGNETIC RESONANCE (MR) GUIDED FOCUSED ULTRASOUND (MRgFUS)

Essential Tremors

Systematic Reviews

A technology assessment was published by Health Quality Ontario (2018). The literature search, conducted through April 2017, identified 9 studies for inclusion: 4 single cohort studies, 2 retrospective chart reviews, 2 uncontrolled prospective studies, and an RCT. The RCT compared MRgFUS with sham treatment, the chart reviews compared MRgFUS with deep brain stimulation and radiofrequency thalamotomy. Study quality was evaluated using the GRADE system. The RCT was rated high quality, the uncontrolled comparative studies were rated very low quality, and the remaining studies were rated low quality. All studies reported tremor severity as an outcome. Pooling of results was not conducted due to heterogeneity in study designs, analyses, and outcomes across the studies. Reviewers determined that, overall, MRgFUS decreased tremor severity and improved QOL. The high-quality RCT by Elias (2016) is discussed below.

Mohammed (2018) conducted a meta-analysis evaluating the use of MRgFUS to treat medicine-refractory essential tremors. The literature search, conducted through August 2017 identified 9 studies (total N=160 patients) for inclusion, 8 of which were also evaluated in...
the Ontario technology assessment. Pooled analyses found significant improvements in the mean percentage change in Clinical Rating Scale for Tremor scores (62.2%) and Quality of Life in Essential Tremor scores (46.5%). Complications included nausea, vomiting, and ataxia, which decreased during the 12-month follow-up.

Randomized Controlled Trials

A single high-quality study, a double-blind, sham-controlled randomized trial by Elias (2016),[14] was identified by the two systematic reviews above. Trial selection criteria included patients with moderate or severe postural or intention tremor of the hand (≥2 on the Clinical Rating Scale for Tremor) and refractory to at least two medical therapies. Patients were randomized to MRgFUS thalamotomy (n=56) or sham treatment (n=20). Outcomes were tremor severity, improvement, and QOL, measured at three months postprocedure. Patients in the treatment group were followed for an additional 12 months. Mean score for hand tremor improved significantly from baseline in the treatment group (47%) compared with the sham group (0.1%) at three months. Change in mean functional improvement score from baseline differed significantly in the MRgFUS group (62%) compared with the sham group (3%) at three months. Change in Quality of Life in Essential Tremor Questionnaire scores also differed significantly in the treatment group compared with the sham group, with the largest improvements experienced in the psychosocial domain. The improvements in hand tremor score, functional improvement, and QOL were maintained at 12 months in the MRgFUS group.

Chang (2018) published results from 67 patients who participated in the open-label extension of the RCT.[15] Because 9 patients from the original trial received additional treatment during the 2-year follow-up, they were excluded from the analysis. Improvements in tremor and disability scores were maintained at the 2-year follow-up (tremor, 19.8±4.9 [baseline] to 8.8±5.0 [at 2 years]; disability, 16.4±4.5 [baseline] to 6.5±5.0 [at 2 years]).

Nonrandomized Studies

A number of nonrandomized studies (N = 11-15) reported on early results from trials implementing MRgFUS as a treatment for essential tremor and were included in the systematic reviews discussed above.[16-18]

Uterine Fibroids

There are several approaches that are currently available to treat symptomatic uterine fibroids: hysterectomy; abdominal myomectomy; laparoscopic and hysteroscopic myomectomy; hormone therapy; uterine artery embolization; and watchful waiting. Hysterectomy and various myomectomy procedures are considered the gold standard treatment. Comparisons to these procedures in well-designed prospective randomized clinical trials are needed to determine whether MRI-guided high intensity focused ultrasound ablation (MRgFUS) results in the same or better health outcomes with respect to long-term treatment effects, recurrence rates and impact on future fertility and pregnancy. The focus of this review is therefore on randomized controlled trials.

Systematic Reviews

A 2013 systematic review, published by Gizzo, identified 38 uncontrolled studies with a total of 2500 patients (mean age 43.67 years) who underwent MRgFUS for treatment of uterine fibroids.[19] All of the published studies included women older than age 18 years with symptomatic uterine fibroids, and most excluded patients who desired future pregnancies. The
The authors of the systematic review did not pool study findings, noting there was no uniform consensus regarding the parameters for evaluating treatment results and considerable variety in the inclusion criteria and follow-up periods. The review confirms the continued absence of published randomized controlled trials on MRgFUS for uterine fibroids.

A 2007 technology assessment published by the Agency for Healthcare Research and Quality (AHRQ) concluded that the strength of the evidence for MRgFUS was weak (defined as evidence from a limited number of studies of weaker design; studies with strong design either have not been done or are inconclusive).[20] The literature included one industry-sponsored prospective case series (n = 109) that was ranked as poor for informing clinical decision-making.[21,22] This study was conducted to support the FDA approval application. The AHRQ report noted that while initial research demonstrated safety and preliminary efficacy, there is a need for comparative study and longer term follow-up.

The report also added the following caution, now that the device is available outside a clinical research setting:

Clinicians need to consider carefully the reality that, now that the systems are in use, care providers are using this new modality to treat fibroids more aggressively than had been allowed during the strict study protocol. The major change in how the systems are now being used is that a greater proportion of the total volume of the fibroid is treated. Therefore, no information exists at present that reflects current practice in terms of procedure-related risks and anticipated outcomes.

This report has now been archived by AHRQ, and there is a continued lack of publication of high-quality evidence from randomized controlled trials. In 2014, Clark published a review of the evidence regarding the role of MRgFUS in the treatment of fibroids and its impact upon future fertility and reproductive outcomes.[23] The authors identified 35 reports of pregnancy after MRgFUS in the available literature; however, additional studies are needed to evaluate the impact of MRgFUS upon future fertility and reproductive outcomes.

Randomized Controlled Trials (RCTs)

In 2015, a pilot sham-controlled RCT with 20 patients was published by Jacoby. The study was designed to determine the feasibility of a full scale randomized study evaluating MRgFUS for treatment of uterine fibroids.[24] The study included premenopausal women with symptomatic uterine fibroids. Women who were pregnant or had a desire for future fertility were excluded. Patients were randomized to MRgFUS with the ExAblate 2000 system (n=13) or a sham treatment in which no thermal energy was delivered (n=7). The investigators did not specify primary outcomes. The sample size of 20 was selected, not to have sufficient statistical power, but to assess the feasibility of a larger trial. All patients assigned to the MRgFUS group and six of seven in the placebo group received their allocated treatment and all treated patients completed three months of follow-up. Patients were unblinded at three months and given the sham group was given the option of active treatment.

QOL outcomes included the Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL), which has subscales including the Symptom Severity Score (SSS) and Health Related Quality of Life (HRQL) score. Other measure was the Medical Outcomes Study (MOS), which has a Mental Component Summary (MCS) and Physical Component Summary (PCS). At both the 4- and 12-week follow-ups, there were no statistically significant differences (at the p<0.05 level) between the MRgFUS and sham groups in the SSS, HRQL,
PCS, or MCS. Change in uterine and fibroid volume, however, differed significantly between groups at 12 weeks. Uterine volume decreased by 17% in the MRgFUS group and by 3% in the sham group (p=0.04). Total fibroid volume decreased 18% in the MRgFUS group and did not change in the sham group (p=0.03). The authors concluded that women are willing to participate in a sham-controlled RCT of MRgFUS and that larger trials are feasible.

Nonrandomized Studies

The “pivotal” study which led to FDA approval of the ExAblate® 2000 device was included in the AHRQ report discussed above.[21,22] Additional study outcomes have been subsequently reported from this same study, although interpretation of any such results is limited by the weak strength of the evidence from the original trial. For example, Taran failed to report on the original primary outcome measure and instead reported findings on a different quality of life measure.[25] The different measures were subject to a multiple comparison bias; a large number of statistical comparisons were done for secondary outcomes, and p-values were not adjusted for increased risk of chance statistical findings.

Another nonrandomized study compared two variations on the MRgFUS procedure.[26] Patients were either treated with the original protocol (33% of fibroid volume with a maximum treatment time of 120 minutes, n=96) or modified protocol (50% treatment volume, 180 minutes maximum treatment time, and a second treatment if within a 14-day period, n=64). Interpretation of these results was limited by 49% loss to follow-up; 55 patients (57%) from the original treatment protocol completed follow-up. Only 21 patients (33%) from the modified protocol group were evaluable at 12-month follow-up.

A prospective registry of pregnancies after MRgFUS was maintained by the manufacturer of the ExAblate device. A 2008 article reported that there were 54 known pregnancies a mean of 8 months after treatment.[27] They included 8 pregnancies from clinical trials designed for women who did not desire pregnancy, 26 pregnancies after commercial treatment, and 20 pregnancies in 17 patients from an ongoing study of MRgFUS in women trying to conceive. Twenty-two of the 54 pregnancies (42%) resulted in deliveries, 11 were ongoing beyond 20 weeks at the time the article was written. There were 14 miscarriages (26%) and 7 elective terminations (13%). Among the 22 live births, the mean birth weight of live births was 3.3 kg, and the vaginal delivery rate was 64%. The article provides initial information on the impact of MRgFUS for uterine fibroids on pregnancy; findings suggest that fertility may be maintained but that the number of cases is too small to draw definitive conclusions. Moreover, the study does not address the possible impact of MRgFUS treatment on the ability to become pregnant.

Other non-comparative, prospective and retrospective case series have been published; however, conclusions concerning health outcomes cannot be reached from these studies due to small study populations, high rate of loss to follow-up, and failure to control for bias which could impact treatment results.[28-34]

Although results from these trials contribute to the body of evidence on MRgFUS, interpretation of such results is limited by the lack of a comparative treatment group, the absence of which does not allow for the comparison of the relative treatment effect of MRgFUS with standard medical alternatives. In addition, there is insufficient evidence on the long-term treatment effects, recurrence rates, and impact on future fertility and pregnancy.

Section Summary
There is insufficient evidence regarding the use of MRgFUS as a treatment of uterine fibroids compared to other established procedures. Evidence from randomized controlled trials is lacking and conclusions concerning the safety and efficacy of MRgFUS cannot be drawn from nonrandomized studies due to methodological limitations such as an inability to isolate treatment effects. Questions remain regarding the durability of MRgFUS treatment or the impact of this treatment upon future fertility.

**Palliative Treatment of Bone Metastases**

The principal outcomes for treatment of pain are symptom relief and improved functional level. Relief of pain is a subjective outcome and can be influenced by nonspecific effects, placebo response, the natural history of the disease, and regression to the mean. Therefore, randomized controlled trials (RCTs) are important to control for nonspecific effects and to determine whether any treatment effect provides a significant advantage over the placebo/sham treatment or other treatments. Appropriate comparison groups depend on the condition being treated and may include placebo/sham stimulation, or medical or surgical management.

Therefore, the assessment of the safety and efficacy of MRgFUS treatment for bone metastases requires large, long-term, randomized controlled trials comparing this technique with the current standard of care for the condition being treated.

**Randomized Controlled Trial (RCT)**

In 2014, Hurwitz published results from a randomized trial that evaluated the safety and efficacy of MRgFUS on palliation of pain due to bone metastases. The study included patients with at least three months of life expectancy who had bone metastases that were painful, despite radiotherapy treatment, or who were unsuitable for or declined radiotherapy. Patients included had to rate tumor pain on a numeric rating scale (NRS) at 4 or higher on a 10-point scale. They could have up to five painful lesions; however, only one lesion was treated and it had to cause at least 2 points greater pain on the NRS than any other lesion. In addition, targeted tumors needed to be device accessible.

Study participants were randomized in a 3:1 ratio to active (n=122) or sham (n=39) MRgFUS treatment. Ten patients in the treatment group and 4 in the sham group did not receive the allocated treatment. An additional 26 patients in the treatment group and 23 in the sham group did not complete the 3-month follow-up. A much larger proportion of the placebo group dropped out; 17 (49%) of 35 who were treated decided to have rescue MRgFUS treatment after lack of response to placebo. A modified intention-to-treat analysis was used that included patients who had at least one MRgFUS or placebo sonication. Missing values were imputed using the last observation carried forward method.

The primary efficacy end point, assessed at three months, was a composite outcome comprised of change in baseline in worst NRS score and morphine equivalent daily dose (MEDD) intake. Patients were considered responders if their worst NRS score decreased by at least 2 points and if their MEDD intake did not increase more than 25% from baseline to three months. NRS score and MEDD intake separately were reported as secondary outcomes.

Seventy-two (64%) of 112 patients in the MRgFUS group and 7 (20%) of 35 patients in the control group were considered responders, as previously defined. The difference between groups was statistically significant (p=0.01), favoring active treatment. When the two measures comprising the primary end point were analyzed separately, there was a statistically significant difference between groups in change in worst NRS score and a nonsignificant difference in NRS score at three months.
change from baseline in pain medication. The NRS score decreased by a mean (SD) of 3.6 (3.1) points in the MRgFUS group and by a mean of 0.7 (2.4) in the placebo group (p<0.01). Change in MEDD was only reported in a figure. Fifty-one (46%) patients in the MRgFUS group and one (3%) in the placebo group experienced at least one adverse event (AE). Most AEs were transient, and the most common was sonication pain, experienced by 36 (32%) patients in the MRgFUS group. In 17 (15%) patients, sonication pain was severe; three patients did not complete treatment due to pain. The most clinically significant AEs that lasted more than a week were third-degree skin burns in one patient (associated with noncompliance with the treatment protocol) and fracture in two patients (one of which was outside the treatment location). Potential limitations of the trial included a nonconventional primary outcome measure and the small initial size of the sham group. Moreover, a large number of sham patients (66%) did not complete the three-month follow-up; the authors did state that this low completion rate was due to lack of response to placebo treatment. Additional randomized studies are required to isolate the treatment effect of MRgFUS upon pain and better characterize the benefit and length of symptom relief with MRgFUS in patients with bone metastases.

**Nonrandomized Studies**

Examples of nonrandomized trials include four small (n=11-31), nonrandomized prospective studies evaluating MRgFUS for the treatment of bone metastases, the majority of which are industry-sponsored.[36-39] Although none reported any treatment-related adverse effects, and all reported improvements in pain and two reported decreases in analgesic use, independent verification of treatment effects with larger groups of patients is needed. At present, results from these trials are not sufficient to reach conclusions regarding the impact of MRgFUS in palliation of pain related to bone metastases due to methodological limitations such as lack of an appropriate control group for comparison.

In addition there have been several small case series published on the use of MRgFUS for treatment of bone metastases. However, these series did not compare the safety and efficacy of this treatment to other treatment options.

**Other Tumors**

MRgFUS is also being studied for several other clinical applications, including the treatment of benign and malignant tumors. As with MRgFUS treatment for uterine fibroids and bone metastases, randomized controlled trials comparing this technique with the current standard of care for the condition being treated are required in order to assess the efficacy of this treatment approach.

**Breast Tumors**

**Nonrandomized Studies**

No controlled studies evaluating MRgFUS for treating breast cancer have been identified in the published literature. Evidence is limited to small case series, examples of which include six feasibility studies that describe preliminary results only.[40-45] Fibroadenoma, ductal carcinomas, adenocarcinomas, and lobular carcinomas were treated. The adverse effects profile includes a few second-degree skin burns, and protocols maintain a roughly 1-cm distance between the tumor margin and the skin or rib cage. Residual tumor in the treated area appears to be a problem, with authors recommending treatment of the entire tumor plus 1 cm of surrounding tissue, as is done in lumpectomy. No long-term outcome studies are available.
As with uterine fibroids, interpretation of these results is limited by the lack of a comparative treatment group.

**Brain Cancer**

*Nonrandomized Studies*

Evidence on MRgFUS in brain cancer is similarly restricted to case series, which include a report of initial findings in 3 patients.[46] The authors reported that it was possible to focus an ultrasound beam into the brain transcranially, and they believe that thermal ablation without overheating the brain is possible; however, substantial technical barriers to using MRgFUS for treating brain tumors remain. Larger and longer comparative trials are needed to establish the use of MRgFUS for treating this indication.

**Prostate Cancer**

*Nonrandomized Studies*

Small (N=1 to 5) feasibility studies regarding the use of MRgFUS in patients with biopsy-proven prostate cancer have demonstrated that the procedure may be performed in this patient population.[47-49] At least one study was conducted using the ExAblate® 2100 System, which is not FDA approved for this indication. Larger and longer comparative trials are needed to establish the use of MRgFUS for treating prostate cancer.

**PRACTICE GUIDELINE SUMMARY**

**AMERICAN CONGRESS OF OBSTETRICS AND GYNECOLOGISTS**

A practice bulletin from American Congress of Obstetrics and Gynecologists (ACOG) considered MRgFUS as an alternative to hysterectomy as a treatment of uterine fibroids, but did not specifically recommend its use, stating:[50]

> Whereas short-term studies show safety and efficacy, long-term studies are needed to discern whether the minimally invasive advantage of MRI-guided focused ultrasound surgery will lead to durable results beyond 24 months. Protocols for treating larger leiomyoma volumes are being studied.

**AMERICAN COLLEGE OF RADIOLOGY**

The 2017 American College of Radiology (ACR) Appropriateness Criteria guidelines regarding the treatment of uterine fibroids[51] mention the use of MRgFUS indicating that, “(t)o date, there is little long-term information on the efficacy of [MRgFUS] technology.” However, the MRgFUS approach is not recommended as treatment for fibroids.

**AMERICAN UROLOGICAL ASSOCIATION**

In 2017, the American Urological Association (AUA) published a joint guideline (with the American Society for Radiation Oncology [ASTRO], and the Society of Urologic Oncology [SUO]) regarding clinically localized prostate cancer.[52] Nearly all recommendations regarding HIFU as a treatment for prostate cancer were Expert Opinion, that is, the committee did not have sufficient evidence to grade the strength of the evidence. Additionally, the following recommendation was made:
Clinicians should advise localized prostate cancer patients considering HIFU that tumor location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence. (Moderate Recommendation; Evidence Level: Grade C)

Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data).

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 3.2018) include high intensity focused ultrasound ablation as a recommended treatment option in the presence of radiation recurrence in a manner that is consistent with the policy criteria.[5]

SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

In 2015, the Society of Obstetricians and Gynaecologists of Canada published a clinical practice guideline entitled “Management of Uterine Fibroids in Women with Otherwise Unexplained Fertility.”[53] The guideline states that there are no studies comparing MRgFUS with myomectomy or in women with fibroids who have infertility as their primary complaint, and thus additional data are needed before the treatment is offered to this patient population.

SUMMARY

HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) ABLATION

It appears that high intensity focused ultrasound (HIFU) ablation may improve overall health outcomes for select men with localized recurrent prostate cancer. Clinical guidelines based on research recommend HIFU for specific patient populations. Therefore, high intensity focused ultrasound may be considered medically necessary to treat localized prostate cancer when policy criteria are met. Due to a lack of research and clinical practice guidelines, HIFU is considered investigational for all other indications that do not meet the policy criteria.

MAGNETIC RESONANCE (MR) GUIDED FOCUSED ULTRASOUND (MRGFUS)

Movement Disorders

It appears that (MRI)-guided focused ultrasound (MRgFUS) may help those with medicine-refractory essential tremor. At least one high quality randomized study has demonstrated improvement in symptoms with MRgFUS treatment and may improve overall quality of life. Therefore, MRgFUS may be considered medically necessary for medicine-refractory essential tremors when policy criteria are met.

Uterine Fibroids

The evidence for MRgFUS in individuals who have uterine fibroids includes a pilot RCT, nonrandomized comparative studies, and case series. The pilot RCT (N=20 patients) reported some health outcomes, but its primary purpose was to determine the feasibility of a larger trial. It did not find statistically significant differences in quality of life outcomes between active and sham treatment groups, but did find lower fibroid volumes after active
treatment. The pivotal Food and Drug Administration trial was not randomized, the clinical significance of the primary outcome was unclear, and there were no follow-up data beyond one year. The limited nature of this evidence-base raises concerns about the reliability and validity of reported findings. In particular, the durability of any early treatment effect with MRgFUS given the potential for regrowth of treated fibroids, is not clearly understood. Therefore, treatment of uterine fibroids with MRgFUS is considered investigational.

Palliative Treatment of Bone Metastases

To date, there are no published randomized controlled trials comparing magnetic resonance imaging (MRI)-guided focused ultrasound (MRgFUS) with a different treatment for pain palliation in patients with bone metastases. There is a single randomized trial comparing MRgFUS to placebo as well as some preliminary reports of safety and efficacy in small numbers of patients; however, this evidence is insufficient, and the impact of MRgFUS on health outcomes remains unknown. Therefore, treatment of pain palliation with bone metastases with MRgFUS is considered investigational.

Other Tumors and other Indications

(MRI)-guided focused ultrasound (MRgFUS) is being investigated for use in several applications that are not currently approved by the FDA. There are some preliminary reports of safety and efficacy in small numbers of patients; however, this evidence is insufficient, and the impact of MRgFUS on health outcomes remains unknown. Due to the lack of evidence from well-designed randomized controlled trials, the use of MRgFUS for the treatment of any condition is considered investigational.

REFERENCES


November 1, 2018

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.


CODES

**NOTE:** There are no specific CPT codes for the use of magnetic resonance–guided high-intensity ultrasound ablation in certain cancers. In these situations an unlisted code would be used based on the anatomic location of the metastasis being treated (eg, 23929 for the clavicle) or perhaps one of the radiation oncology unlisted codes (eg, 77299 or 77499).

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>0071T</td>
<td>Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume of less than 200 cc of tissue</td>
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<tr>
<td></td>
<td>0072T</td>
<td>total leiomyomata volume greater or equal to 200 cc of tissue</td>
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<tr>
<td></td>
<td>0398T</td>
<td>Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed</td>
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<tr>
<td></td>
<td>23929</td>
<td>Unlisted procedure, shoulder</td>
</tr>
<tr>
<td></td>
<td>58578</td>
<td>Unlisted laparoscopy procedure, uterus</td>
</tr>
<tr>
<td></td>
<td>58579</td>
<td>Unlisted hysteroscopy procedure, uterus</td>
</tr>
<tr>
<td>HCPCS</td>
<td>C9734</td>
<td>Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance</td>
</tr>
<tr>
<td></td>
<td>C9747</td>
<td>Ablation of prostate, transrectal, high intensity focused ultrasound (HIFU), including imaging guidance</td>
</tr>
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</table>

**Date of Origin:** October 2004
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

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

Notes:

- 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.

I. Single photon emission computed tomography (SPECT) of the brain is considered investigational for the following conditions:
<p>| | |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>A.</td>
<td>Attention-deficit/hyperactivity disorder (ADHD)</td>
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<tr>
<td>B.</td>
<td>Autism</td>
</tr>
<tr>
<td>C.</td>
<td>Behavioral health disorders (including, but not limited to bipolar disorder, major depressive disorder, schizophrenia, and personality disorders)</td>
</tr>
<tr>
<td>D.</td>
<td>Cerebrovascular disease (including stroke, transient ischemic attack, and subarachnoid hemorrhage)</td>
</tr>
<tr>
<td>E.</td>
<td>Chronic fatigue syndrome</td>
</tr>
<tr>
<td>F.</td>
<td>Dementias (including Alzheimer’s, vascular dementia, frontal temporal dementia, Pick’s disease and dementia with Lewy bodies)</td>
</tr>
<tr>
<td>G.</td>
<td>Encephalopathy (including but not limited to Lyme, Wernicke’s, hypoglycemia, and hypoxic-ischemic encephalopathy)</td>
</tr>
<tr>
<td>H.</td>
<td>Motor neuron disorders [including amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis, and progressive (spinal) muscular atrophy]</td>
</tr>
<tr>
<td>I.</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>J.</td>
<td>Parkinsonian syndromes and essential tremor</td>
</tr>
<tr>
<td>K.</td>
<td>Substance-related disorders (including alcohol)</td>
</tr>
<tr>
<td>L.</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>II.</td>
<td>SPECT of the brain for indications other than those listed above may be considered medically necessary.</td>
</tr>
</tbody>
</table>

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

**POLICY GUIDELINES**

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for testing

**CROSS REFERENCES**

1. [Dopamine Transporter Single-Photon Emission Computed Tomography (DAT-SPECT)](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:

- Adrean (iodobenzene I-123)
- Technetium TC-99m (mebrofenin)
- I-123 isopropylidiomethaphetamine (IMP, Spectamine)
- Tc-99m HMPAO (hexamethyl propylamine oxime, Ceretec)
- Tc-99m ECD (ethyl cysteinate dimer, Neurolite)
- thallium 201 diethylthiocarbamate (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

Mutoh (2018) performed a cohort study to analyze the ability of SPECT to predict prognosis in 29 patients following aneurysmal subarachnoid hemorrhage (SAH).[65] Patients who had...
undergone surgery for ruptured anterior communicating artery aneurysms underwent routine measurements using technetium-99 m hexamethyl propyleneamine oxine SPECT on days four and 14 after SAH. SPECT results were analyzed by three-dimensional stereotactic surface projection (3D-SPP) and an age-matched normal database (NDB) was used as a reference. The analysis showed that cortical hypoperfusion around the surgical site in bilateral frontal lobes was evident on day four (p<0.05 vs NDB), and was improved significantly on day 14. The recovery was significantly less complete in patients with poor clinical grades (p<0.05) and patients presenting symptoms attributable to delayed cerebral ischemia (p<0.05). SPECT results indicating mild to moderate recovery were independently associated with poor functional outcome at three months in a multivariate analysis (p=0.014; odds ratio [OR], 2.5; 95% confidence interval [CI], 1.93-3.31)

Kincaid (2009) 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.[56] TCD was able to predict vasospasm with an OR of 27 (95% 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 OR 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

Systematic Reviews

Archer (2015) 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.[57] Five cohort studies (two retrospective cohort studies and three prospective) were included to assess the diagnostic capabilities of SPECT in patients with suspected dementia.[58,59] 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.[60] 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”. [61] 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. 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 in differentiating between AD and non-AD dementia in post-mortem samples.

Davison and O'Brien (2014) 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). 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. 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 (2013) 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. 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 five
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

In a 2017 retrospective study, Höller compared SPECT with EEG and with a combination of
SPECT and EEG in patients with diagnosed dementias. Standard clinical
electroencephalography (EEG) and 99mTc-hexamethyl-propylene-aminoxime (HMPAO)-
SPECT were used to assess 39 patients with Alzheimer’s dementia (AD), 69 patients with
depressive cognitive impairment (DCI), 71 patients with amnestic mild cognitive impairment
(aMCI), and 41 patients with amnestic subjective cognitive complaints (aSCC). Patient groups
were classified pairwise (using a linear support vector machine) separately for each biomarker
and then again for each EEG biomarker combined with SPECT. HMAO-SPECT alone was not
able to reliably identify the individual disorders, but a combination of HMAO-SPECT with EEG
outperformed EEG alone and was able to classify aSCC verus AD, aMCI versus AD, and AD
versus DCI.

Brayet (2017) analyzed the ability of SPECT scans to differentiate between AD patients and
healthy controls. Eight aMCI subjects and 16 age-matched controls underwent SPECT
scans during wakefulness and during REM sleep. A significant decrease in perfusion in the anterior cingulate cortex was reported in aMCI cases during wakefulness (p<0.024), and a larger decrease was reported during REM sleep (p<0.001).

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.[69] 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 (2014) compared the diagnostic ability of perfusion SPECT with FDG-PET to differentiate between Alzheimer and Lewy body dementias.[70] 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 (2014) compared the ability of perfusion SPECT with 3D arterial spin-labeled brain perfusion imaging to diagnose AD.[71] 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 (2013) 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).[72] 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 (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

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Assadi (2010) 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. MRI was performed on 16 patients (13 women and three 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.

PARKINSONIAN SYNDROMES AND ESSENTIAL TREMOR

Systematic Reviews

Sharifi (2014) performed a systematic review of the role of neuroimaging techniques in the diagnosis and evaluation of essential tremor. The reviewers included two small studies using SPECT to determine rCBF at rest. 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.

In a 2007 systematic review of the literature on diagnostic accuracy of SPECT in parkinsonian syndromes, Vlaar included 15 small case series that used SPECT with post-synaptic tracers, which measure dopamine receptor density. When SPECT was used to differentiate between PD and essential tremor (ET), two studies were included and the pooled OR 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 OR 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 recommends the following steps for biomarker validation in psychiatric disorders:

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[78] 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[79] 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[80] 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
- 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 2017 ACR Appropriateness Criteria® for cranial neuropathy[81] indicated that the use of SPECT in studying olfactory dysfunction remains “largely investigative and are not generally used in routine evaluations.”

The 2016 ACR-Society for Pediatric Radiology (SPR)[82] 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.

For all other uses for single photon emission computed tomography (SPECT) of the brain, there is enough research to show that SPECT improves health outcomes. Therefore, all other uses of SPECT for the brain may be considered medically necessary.

**REFERENCES**

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