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.

Single photon emission computed tomography (SPECT) is considered investigational for the following conditions:

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

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

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

CROSS REFERENCES
1.  Dopamine Transporter Single-Photon Emission Computed Tomography, Radiology, Policy No. 57

BACKGROUND

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

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

REGULATORY STATUS

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

**EVIDENCE SUMMARY**

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

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

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

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

**CEREBROVASCULAR DISEASE**

**Nonrandomized Studies**

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

**DEMENTIAS**
Archer et al. performed a Cochrane systematic review in 2015 to assess the diagnostic accuracy of cerebral blood flow (rCBF) SPECT for diagnosing frontal temporal dementia (FTD) in populations with suspected dementia settings and the ability of SPECT to differentiate between FTD from other dementia subtypes.\[56] Five cohort studies (two retrospective cohort studies and three prospective) were included to assess the diagnostic capabilities of SPECT in patients with suspected dementia.\[57,58] 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.\[59] 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”.\[60] 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. \[59,61] The diagnostic accuracy of HMPAO-SPECT was determined by one study by Bonte et al., which found that SPECT had a sensitivity of 93% and a specificity of 85% in differentiating between AD and non-AD dementia in post-mortem samples.\[62]

Davison and O'Brien performed a systematic review in 2014 comparing FDG-PET and rCBF SPECT in the diagnosis of neurodegenerative dementias, including nine studies that directly compared the two imaging modalities (N=117 subjects with AD, 46 subjects with other dementias and 100 controls).\[63] 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.\[45,64] Published studies of SPECT sensitivities ranged from 65-85% for diagnosing Alzheimer's disease (AD) and specificities (for other neurodegenerative dementias) of 72-87%. PET sensitivities and specificities were slightly higher than SPECT, ranging from 75-99% and 71-93%, respectively. Both of these modalities are therefore just as sensitive at predicting and diagnosing AD as the current standard for clinical diagnosis, NINCDS-ADRDA, which has sensitivity ranging from 65-96%. Limitations of the included studies listed were small sample size, poorly matched control groups, and heterogeneity in study design.

Yeo et al. performed systematic review of the diagnostic utility of HMPAO SPECT in neurodegenerative dementia, and pooled studies with a clinical diagnosis and those using 99mTc-HMPAO SPECT in a meta-analysis.\[65] Forty-nine studies were included in the review; AD versus FTD (n = 13), AD versus VD (n = 18), AD versus DLB (n = 5), and AD versus NC (n = 18). However, the majority of these included studies had small sample sizes, with only 5
studies having more than 100 subjects. The reviewer reported sensitivity and specificity of 99mTc-HMPAO-SPECT in distinguishing clinically diagnosed AD from FTD are 79.7 and 79.9%, respectively, AD from VD are 74.5 and 72.4%, AD from DLB are 70.2 and 76.2%, and AD from NC are 76.1 and 85.4%. Limitations of this analysis include small numbers of studies for each diagnostic comparison group and high methodological heterogeneity between studies. The reviewers concluded that SPECT is valuable in differentiating Alzheimer’s disease from frontotemporal dementia and normal controls, but should only be used in with clinical information and other test results.

**Nonrandomized Studies**

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

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

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

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

MULTIPLE SCLEROSIS

Nonrandomized Studies

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

ESSENTIAL TREMOR

Systematic Reviews

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

PARKINSONIAN SYNDROMES

Systematic Reviews

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

PRACTICE GUIDELINE SUMMARY

AMERICAN PSYCHIATRIC ASSOCIATION (APA)

An APA 2012 consensus report from the APA work group on neuroimaging markers of psychiatric disorders,[74] recommends the following steps for biomarker validation in psychiatric disorders:
1. There should be at least two independent studies that specify the biomarker’s sensitivity, specificity, and positive and negative predictive values;
2. Sensitivity and specificity should be no less than 80%; positive predictive value should approach 90%;
3. The studies should be well powered, conducted by investigators with expertise to conduct such studies, and the results published in peer-reviewed journals;
4. The studies should specify type of control subjects, including normal subjects and those with a dementing illness but not AD; and
5. Once a marker is accepted, follow-up data should be collected and disseminated to monitor its accuracy and diagnostic value.

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

**AMERICAN COLLEGE OF RADIOLOGY (ACR)**

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

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

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

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

- Dementia and movement disorders (consider for problem solving)
- Probable or possible Alzheimer’s disease
- Suspected frontotemporal dementia
- Suspected vascular dementia
- Suspected normal pressure hydrocephalus
- Suspected Huntington disease
- Clinical features suggestive of neurodegeneration with brain iron accumulation
• Motor neuron disease (consider for problem solving)
• Parkinson disease with typical clinical features and responsive to levodopa
• Parkinsonian syndrome with atypical clinical features not responsive to levodopa.

A rating of 4 or 5 (“may be appropriate”) was assigned to the following conditions:

• Suspected prion disease (Creutzfeldt-Jakob, iatrogenic, or variant)
• Suspected dementia with Lewy bodies
• Parkinson disease with typical clinical features and responsive to levodopa.

The 2016 ACR-Society for Pediatric Radiology (SPR)\textsuperscript{[78]} developed a practice parameter that states SPECT brain perfusion is clinically indicated for the following:

• Evaluating patients with suspected dementia
• Localizing epileptic foci preoperatively
• Diagnosing encephalitis
• Monitoring and assessing vascular spasm following subarachnoid hemorrhage
• Mapping of brain perfusion during interventions
• Detecting and evaluating cerebrovascular disease
• Predicting the prognosis of patients with cerebrovascular accidents
• Corroborating the clinical impression of brain death

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

**SUMMARY**

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

**REFERENCES**


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


77. American College of Radiology. ACR Appropriateness Criteria® Dementia and Movement Disorders. Reviewed 2015. [cited 04/04/2017]; Available from: [https://acsearch.acr.org/docs/69360/Narrative/](https://acsearch.acr.org/docs/69360/Narrative/)

## CODES

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