Medical Policy Manual

**Topic:** Single Photon Emission Computed Tomography (SPECT) of the Brain  
**Date of Origin:** March 2005

**Section:** Radiology  
**Last Reviewed Date:** March 2016

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**IMPORTANT REMINDER**

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

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

**DESCRIPTION**

Single photon emission computed tomography (SPECT) is a nuclear imaging technique that is used to visualize functional information about body organs, including the brain. 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.[1-4] 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)

**MEDICAL POLICY CRITERIA**

**Note:**

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

I. Single photon emission computed tomography (SPECT) of the brain is considered **investigational** for the following conditions:

- Behavioral health disorders (including, but not limited to bipolar disorder, major depressive disorder, schizophrenia, and personality disorders)
- Attention-deficit/hyperactivity disorder (ADHD)
- Substance-related disorders (including alcohol)
- Autism
- Traumatic brain injury
- Cerebrovascular disease (including stroke, transient ischemic attack, and subarachnoid hemorrhage)
- Encephalopathy
- Chronic fatigue syndrome
- Dementias (including Alzheimer’s, vascular dementia, frontal temporal dementia, Pick’s disease and dementia with Lewy bodies)
- Parkinsonian syndromes and essential tremor
- Motor neuron disorders [including amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis, and progressive (spinal) muscular atrophy]
- Multiple sclerosis
- Epilepsy or seizure disorders

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

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.

Literature Appraisal

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/cohorts that allow for limited evidence of the clinical utility of SPECT. 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 will not be described here.

The evidence summarized below will focus on recent systematic reviews and comparative studies that investigate the utility of SPECT compared to other imaging modalities and/or standard clinical diagnostic 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. 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

Systematic Reviews

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. Five cohort studies (two retrospective cohort studies and three prospective) were included.
to assess the diagnostic capabilities of SPECT in patients with suspected dementia. 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. 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”. 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 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 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. 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

O’Brien et al. 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 et al. 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 et al. performed a multicenter prospective cohort study to examine the ability of \(^{123}\)I-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 \(^{123}\)I-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.[73] 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
Sharifi et al. 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.

Parkinsonian Syndromes

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. 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.

Epilepsy and Seizure Disorders

In 2012, Burch et al. conducted a systematic review to determine which noninvasive technologies should be used in the workup for epilepsy surgery to identify structural or functional abnormalities to help locate the site of seizure onset. The review focused on patients for whom there was insufficient confidence, in either the decision to go to surgery or the site at which surgery should be conducted, after the initial clinical examination. The majority of the studies identified were single-gate diagnostic accuracy studies; none were randomized controlled trials, and only one reported the effect of the test results on the decision-making process. It became apparent that the data derived from diagnostic accuracy studies could not be used to answer the review question. This article focuses on the methods used to extract data from the diagnostic accuracy studies, the difficulties interpreting the resulting data, why such studies are not an appropriate study design in this setting, and how the evidence-base can be improved.

In 2010, Lai et al. published a review evaluating neuroimaging techniques in patients with epilepsy. Authors included 52 articles in their review; however, no RCTs were identified. SPECT was reported as a complementary imaging technique for defining an epileptogenic zone. Authors included 52 articles in their review; however, no RCTs were identified. SPECT was reported as a complementary imaging technique for defining an epileptogenic zone but the study did not evaluate how this added imaging was used to improve health outcomes or alter treatment decisions. Additional systematic reviews were identified that evaluated a variety of imaging techniques for localizing epileptic seizures prior to surgery. However, due to a lack of RCTs and significant study heterogeneity conclusions cannot be drawn regarding the predictive value of SPECT in patients with refractory epilepsy being considered for surgery.
In 2006, Whiting et al. performed a systematic review to assess the effectiveness, accuracy, and predictive value of neuroimaging of the cerebral cortex to visualize seizure foci in patients with refractory epilepsy being considered for surgery. Authors included articles that used SPECT (n=39) in their review; as well as MRI (n=30), PET (n=18), SISCOM (n=7), MRS (n=6) and CT (n=5); however, no RCTs were identified. Due to the degree of heterogeneity between SPECT studies, statistical pooling and analysis could not be performed. The authors reported that SPECT generally had more correctly localizing (70--100%) and fewer non-localizing (0--7%) scans than other techniques evaluated in patients with temporal lobe epilepsy, but felt that both SPECT and CT were relatively poor at localizing the seizure focus.

**Randomized Controlled Trials (RCTs)**

In 2011, Velasco and colleagues published an assessment of the use of SPECT to evaluate and diagnose patients with mesial temporal lobe epilepsy and hippocampal sclerosis (MTLE-HS). Patients were randomized to SPECT (n=124) or non-SPECT (n=116) and primary endpoints were the proportion of patients with invasive EEG studies and those offered surgery. There were no differences between groups regarding the proportion of patients offered surgery or seizure-free after surgery. The authors concluded that SPECT did not add localizing value which altered surgical decisions or outcomes in patients with MTLE-HS.

**Clinical Practice Guidelines**

**American Academy of Neurology (AAN)**

The AAN practice parameters for the diagnosis of dementia was reaffirmed in 2010 and concluded, “For patients with suspected dementia, SPECT cannot be recommended for routine use in either initial or differential diagnosis as it has not demonstrated superiority to clinical criteria.”

**American Psychiatric Association (APA)**

The APA offers a 2012 consensus report of the APA work group on neuroimaging markers of psychiatric disorders. The report 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[85] 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[86] indicated that SPECT with uses 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 2014 ACR Appropriateness Criteria® for dementia and movement disorders[87] provides guidance on the use of SPECT. A rating of 2 or 3 (“usually not appropriate”) was assigned to the following conditions:
- Probable or possible Alzheimer’s disease
- Suspected frontotemporal dementia
- Suspected vascular dementia
- Suspected prion disease (Creutzfeldt-Jakob, iatrogenic, or variant)
- Suspected normal pressure hydrocephalus
- Suspected Huntington disease
- Clinical features suggestive of neurodegeneration with brain iron accumulation
- Motor neuron disease
- 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 dementia with Lewy bodies
- Parkinson disease with typical clinical features and responsive to levodopa.

The 2012 ACR consensus guidelines on SPECT brain perfusion[88] indicates SPECT can be utilized for evaluating patients with suspected dementia; however, SPECT has not been fully characterized for neuropsychiatric disorders.[83,84,88-91]

Summary
The current evidence base is insufficient to permit conclusions regarding the benefits of single photon emission computed tomography (SPECT) of the brain in the evaluation, diagnosis or treatment for a variety of neurologic, psychiatric, psychological, and other nononcologic indications. Additional studies are needed from well-designed randomized controlled trials that investigate the clinical utility of SPECT compared to other imaging modalities and/or standard clinical diagnostic criteria. No evidence-based clinical practice guidelines recommend the use of SPECT of the brain for the investigational indications described in this policy. 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.

REFERENCES


78. Lai, V, Mak, HK, Yung, AW, Ho, WY, Hung, KN. Neuroimaging techniques in epilepsy. *Hong Kong medical journal = Xianggang yi xue za zhi / Hong Kong Academy of Medicine*. 2010 Aug;16(4):292-8. PMID: 20683073


CROSS REFERENCES

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

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