Miscellaneous (Non-cardiac, Non-oncologic) Applications of Positron Emission Tomography

Description

Positron emission tomography (PET) images biochemical and physiological functions by measuring concentrations of radioactive chemicals that are partially metabolized in the body region of interest. Radiopharmaceuticals used for PET are generated in a cyclotron or nuclear generator and introduced into the body by intravenous injection or by respiration.

Background

A variety of PET radiopharmaceuticals have been investigated; however, only a few have received approval by the U.S. Food and Drug Administration (FDA) for clinical use. The scanners used for PET imaging are somewhat similar to those used for x-ray computed tomography (CT), but PET requires complicated technology and computerized mathematical models of physiologic functions and tracer kinetics for the generation of images.

Important Note: This policy only addresses the use of radiotracers detected with the use of dedicated full-ring PET scanners. Radiotracers such as fluorodeoxyglucose (FDG) may be detected using single-photon emission computed tomography (SPECT) cameras, a hybrid PET/SPECT procedure that may be referred to as FDG-SPECT or molecular coincidence detection. The use of SPECT cameras for PET radiotracers presents unique issues of diagnostic performance and is not considered in this policy.

Regulatory Status

The 1997 FDA Modernization Act established FDA authority over the safety and effectiveness of locally manufactured radiotracers and developed streamlined regulations for good manufacturing practices (GMP) with which each PET facility must comply.

The following radiotracers have been approved by the FDA:

- $^{18}$F-FDG for evaluation of glucose metabolism in oncology
- $^{18}$F-FDG for evaluation of myocardial hibernation
- $^{13}$N-ammonia for evaluation of myocardial blood flow
• $^{82}$Rb (rubidium) chloride injection (NDA-19-414) was approved in 1989 “for assessing regional myocardial perfusion in the diagnosis and localization of myocardial infarction.”

• $^{18}$F FDG (NDA 20-306) was approved in 1994 for “the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.”

• $^{11}$C-choline injection (NDA 203-155) was approved in 2012 for “PET imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, CT, or MRI.”

• $^{18}$F sodium fluoride injection (NDA 17-042) was approved in 1972 for “injection as a bone imaging agent to define areas of altered osteogenic activity.” The original company ceased making this drug product in 1975, and it is now being marketed again by PETNET Solutions (a Siemens company).

In September 2005, the FDA issued a draft rule and draft guidance on current good manufacturing practice (CGMP) for PET drug products. The final CGMP regulation for the production of PET drugs was issued on December 9, 2009 and took effect on December 12, 2011. More detailed information available online at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm.

**Related Policies**

6.01.20 Cardiac Applications of Positron Emission Tomography Scanning
6.01.26 Oncologic Applications of Positron Emission Tomography Scanning
6.01.51 Interim PET Scanning in Oncology to Detect Early Response During Treatment
6.01.55 Beta Amyloid Imaging with Positron Emission tomography (PET) for Alzheimer’s Disease

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Positron emission tomography (PET) using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) may be considered **medically necessary** in:

1. the assessment of selected patients with epileptic seizures who are candidates for surgery (see Policy Guidelines)
2. the diagnosis of chronic osteomyelitis.

The use of PET for all other miscellaneous indications is **not medically necessary**, including, but not limited to:

**CNS Diseases**

Autoimmune disorders with CNS manifestations, including:

• Behcet’s syndrome
• lupus erythematosus
Cerebrovascular diseases, including:
- arterial occlusive disease (arteriosclerosis, atherosclerosis)
- carotid artery disease
- cerebral aneurysm
- cerebrovascular malformations (AVM and Moya-Moya disease)
- hemorrhage
- infarct
- ischemia

Degenerative motor neuron diseases, including:
- amyotrophic lateral sclerosis
- Friedreich's ataxia
- olivopontocerebellar atrophy
- Parkinson's disease
- progressive supranuclear palsy
- Shy-Drager syndrome
- spinocerebellar degeneration
- Steele-Richardson-Olszewski disease
- Tourette's syndrome

Dementias, including:
- Alzheimer's disease
- multi-infarct dementia
- Pick disease
- frontotemporal dementia
- dementia with Lewy-Bodies
- presenile dementia

Demyelinating diseases, such as multiple sclerosis

Developmental, congenital, or inherited disorders, including:
- adrenoleukodystrophy
- Down syndrome
- Huntington's chorea
kinky-hair disease (Menkes’ syndrome)
- Sturge-Weber syndrome (encephalofacial angiomatosis) and the phakomatoses

Miscellaneous
- chronic fatigue syndrome
- sick building syndrome
- post-traumatic stress disorder

Nutritional or metabolic diseases and disorders, including:
- acanthocytosis
- hepatic encephalopathy
- hepatolenticular degeneration
- metachromatic leukodystrophy
- mitochondrial disease
- subacute necrotizing encephalomyelopathy

Psychiatric diseases and disorders, including:
- affective disorders
- depression
- obsessive-compulsive disorder
- psychomotor disorders
- schizophrenia

Pyogenic infections, including:
- aspergillosis
- encephalitis

Substance abuse, including the CNS effects of alcohol, cocaine, and heroin

Trauma, including brain injury and carbon monoxide poisoning

Viral infections, including:
- acquired immune deficiency syndrome (AIDS)
- AIDS dementia complex
- Creutzfeldt-Jakob syndrome
- progressive multifocal leukoencephalopathy
- progressive rubella encephalopathy
- subacute sclerosing panencephalitis

- Mycobacterium infection
- Migraine
- Anorexia nervosa
- Assessment of cerebral blood flow in newborns
  - Vegetative versus “locked-in state”

Pulmonary Diseases
- Adult respiratory distress syndrome
- Diffuse panbronchiolitis
- Emphysema
- Obstructive lung disease
- Pneumonia

Musculoskeletal Diseases
- Spondylodiscitis
- Joint replacement follow-up

Other
- Giant cell arteritis
- Vasculitis
- Vascular prosthetic graft infection
- Inflammatory bowel disease
- Sarcoidosis
- Fever of unknown origin
- Inflammation of unknown origin

Policy Guidelines

In patients with epileptic seizures, appropriate candidates are patients with complex partial seizures that have failed to respond to medical therapy and who have been advised to have a resection of a suspected epileptogenic focus located in a region of the brain accessible to surgery. Conventional techniques for seizure localization must have been tried and provided data that suggested a seizure focus but were not sufficiently conclusive to permit surgery. In addition, the purpose of the positron emission tomography (PET) examination should be to avoid subjecting the patient to extended preoperative electroencephalographic recording with implanted electrodes or to help localize and minimize the number of sites for implanted electrodes to reduce the morbidity of that procedure.
Rationale

Literature Review

This policy was in part based on 4 Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) Assessments on miscellaneous applications of PET. (1-4) In terms of miscellaneous (ie, non-cardiac, non-oncologic) applications of PET, PET using fluorodeoxyglucose (FDG) was initially considered medically necessary for the assessment of selected patients with epileptic seizures and investigational for other indications. The key literature identified in updated literature reviews is described next.

Epilepsy

A 2007 meta-analysis on the use of FDG-PET for preoperative evaluation of patients with temporal lobe epilepsy found that ipsilateral PET hypometabolism had a predictive value for a good outcome of 86%. The authors noted, however, the difficulty of the analysis because of differences in study designs and lack of precise patient data, which made the incremental value of PET unclear. PET may not add value for patients well-localized by ictal scalp electroencephalography and magnetic resonance imaging (MRI). (5) A 2012 meta-analysis on predictors of long-term seizure freedom after surgery for frontal lobe epilepsy found that PET findings did not predict seizure freedom. (6)

Chronic Osteomyelitis

In 2005, Termaat et al published a systematic review and meta-analysis of diagnostic imaging to assess chronic osteomyelitis. (7) The authors reviewed studies on 6 imaging approaches to chronic osteomyelitis, including FDG-PET and concluded that PET was the most accurate mode (pooled sensitivity: 96%; 95% confidence interval [CI] 88% to 99%; pooled specificity, 91% 95% CI, 81% to 95%) for diagnosing chronic osteomyelitis. Leukocyte scintigraphy was adequate in the peripheral skeleton (sensitivity, 84%; 95% CI, 72% to 91%; specificity: 80% 95% CI, 61% to 91%) but was inferior in the axial skeleton (sensitivity: 21%; 95% CI, 11% to 38%; specificity: 60%; 95% CI, 39% to 78%). The assessment of PET was based on 4 prospective, European studies published between 1998 and 2003, with a total of 1660 patients. However, the study populations varied and included the following: 1) 57 patients with suspected spinal infection referred for FDG-PET and who had previous spinal surgery but not “recently” (8); 2) 22 trauma patients scheduled for surgery who had suspected metallic implant-associated infection (9); 3) 51 patients with recurrent osteomyelitis or osteomyelitis symptoms for more than 6 weeks, 36 in the peripheral skeleton and 15 in the central skeleton (10); and 4) 30 consecutive non-diabetic patients referred for possible chronic osteomyelitis. (11) The results appeared to be robust across fairly diverse clinical populations, which strengthen the conclusions.

In a 2013 systematic review and meta-analysis of 9 studies, FDG-PET and PET/CT was found to be useful for suspected osteomyelitis in the foot of patients with diabetes. (12) A meta-analysis of 4 studies found the sensitivity was 74% (95% CI, 60% to 85%), specificity 91% (95% CI, 85% to 96%), positive likelihood ratio 5.56 (95% CI, 2.02 to 15.27), negative likelihood ratio 0.37 (95% CI, 0.10 to 1.35), and diagnostic odds ratio 16.96 (95% CI, 2.06 to 139.66). The area under the summary receiver-operating characteristic (ROC) curve was 0.874.
Alzheimer’s Disease and Dementia

The Centers for Medicare and Medicaid Services (CMS) issued a decision memorandum on April 16, 2003, that would not support coverage of FDG-PET in Alzheimer’s disease (AD) because the evidence did not demonstrate its use for improved patient outcomes. This decision was based, in part, on a technology assessment conducted at Duke University through the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (13). This assessment used decision-analysis modeling to examine whether the use of FDG-PET would improve health outcomes when used for diagnosis of AD in 3 clinical populations: patients with dementia, patients with mild cognitive impairment, or subjects with no symptoms but a first-degree relative with AD. PET was considered to have an 88% sensitivity (95% CI, 79% to 94%) and 87% specificity (95% CI, 77% to 93%) for diagnosing AD. The report concluded that outcomes for all 3 groups of patients were better if all patients were treated with agents such as cholinesterase inhibitors rather than using FDG-PET to select patients for treatment based on PET results, because the complications of treatment were relatively mild, and treatment was considered to have some degree of efficacy in delaying the progression of AD. Thus, the adverse effect of not treating subjects with AD who had false-negative PET results was influential in this analysis. However, this conclusion was sensitive to the toxicity associated with treatment.

In October 2003, CMS agreed to reconsider its policy on PET for AD and dementia. On September 15, 2004, Medicare made public its final decision memorandum announcing a positive national coverage decision for a subset of patients “with a recent diagnosis of dementia and documented cognitive decline of at least 6 months, who meet diagnostic criteria for both AD and frontotemporal dementia, who have been evaluated for specific alternative neurodegenerative diseases or causative factors, and for whom the cause of the clinical symptoms remains uncertain.” (14) For its reconsideration, CMS requested an update of the original AHRQ assessment which concluded that no new publications provided direct evidence to evaluate the use of PET to either differentiate among different types of dementia or to identify those patients with mild cognitive impairment who were at greatest risk to progress to AD. (15) Additionally, Medicare considered a consensus report by the Neuroimaging Work Group of the Alzheimer’s Association (16) and proceedings of an expert panel discussion of neuroimaging in AD, convened by the National Institute of Aging and Medicare. (17)

In 2005, a meta-analysis compared the ability of FDG-PET, SPECT, and structural MRI to predict patients’ conversion from mild cognitive impairment (MCI) to AD. (18) Using 24 articles identified among studies published between 1990 to April 2008 (6 on FDG-PET, published 2001-2005), the authors found no statistically significant difference among the 3 modalities in pooled sensitivity, pooled specificity, or negative likelihood ratio, FDG-PET had the highest odds ratio and positive likelihood ratio. However, there was strong evidence of between-study heterogeneity and marked asymmetry in the funnel plot (with studies missing from the bottom left quadrant), reducing confidence in the results. Efforts to identify sources of heterogeneity (eg, publication year, age, male-female ratio, follow-up interval, years of education, mean mini-mental state examination [MMSE] score at baseline) yielded no significant results; only the imaging technique was associated with the log odds ratio. In an apparent error, the article states that “[N]o statistically significant difference was found (p >0.05) for each technique in pooled sensitivity and LR-”[emphasis added]. Also, in Table 5, the odds ratio for FDG-PET is reported as 40.146 (95% CI, 18.53 to 6.97). The last number appears to be incorrect.)
In a quasi-systematic review (quality assessment of included studies was not reported), Davison et al (2014) reported diagnostic performance of FDG-PET in 3 studies (total N=197) that used histopathology as reference standard. (19) In patients with or without a clinical diagnosis of AD, sensitivity was 84%, and specificity was 74%; in patients with memory loss or dementia, sensitivity was 94%, and specificity was approximately 70%. In comparison, in 173 patients with memory loss or dementia (3 studies), sensitivity and specificity of SPECT were 63% to 87% and 73% to 90%, respectively. For predicting conversion from MCI to AD, sensitivity and specificity of PET were 82% to 89% and 78% to 85%, respectively, compared with 81% to 84% and 70% to 90%, respectively, for SPECT. Information about health outcomes in patients undergoing PET or SPECT imaging was not reported.

Research continues on efforts to use PET to identify AD and differentiate it from other types of dementia. For example, a 2008 multicenter, international study with 548 patients, including normal patients and those with MCI, AD, frontotemporal dementia, and dementia with Lewy bodies, used Neurological Statistical Image Analysis (Neurostat, University of Washington) to process the results. (20) Excluding the patients with MCI, the sample was split in half, with key PET findings identified on half of the data set and validated on the second half of the data set. Disease-specific PET patterns correctly classified 94% of unimpaired patients, 95% AD, 92% dementia with Lewy bodies, 94% frontotemporal dementia (p<0.001). PET patterns were also 98% sensitive and 92% specific (p<0.001) in distinguishing MCI from unimpaired patients. While interesting, these findings need to be replicated on a less selected sample, ie, one that includes patients with MCI. Also, the reference standard used was clinical diagnosis, so the incremental value, if any, of PET imaging over clinical judgment alone could not be determined. More generally, evidence of clinical utility would require demonstrating that PET improved diagnostic accuracy and that earlier or more accurate diagnosis led to treatment changes that improved health outcomes.

One of the challenges in evaluating the use of PET to distinguish among dementias is to identify what serves as the reference standard. Durand-Martel et al noted in 2010 that the sensitivity of clinical diagnosis for AD varies between 75% and 98%, with an average of 82%. (21) Therefore, comparing PET results to clinical diagnosis can be confounded by the fact that the clinical diagnosis itself may not be accurate. Durand-Martel et al asserted that autopsy results should serve as the reference standard in studies on the use of FDG-PET for dementia; they identified only 5 studies with 20 patients or more in which results of both FDG-PET imaging and autopsy were presented.

There is also research on alternative radiotracers to FDG in identifying AD. In particular, there is interest in amyloid PET tracers, because beta amyloid is the principal component of AD plaques in the brain. (22) (See Policy 6.01.55, Beta Amyloid Imaging with Positron Emission Tomography for Alzheimer Disease.)

Another recent research interest is the potential use of PET scan results as a biomarker for progression to AD. It is difficult to evaluate treatments that may prevent or delay the onset of dementia in individuals with MCI because a relatively small number of study participants will progress to AD during the follow-up period. A 2011 study by Herholz et al in the U.K. used a quantitative PET score previously devised by this research group to evaluate disease progression; a software program was available to calculate the score. (23) The study included 94 patients with MCI, 40 patients with mild AD and 44 healthy
controls. Participants received 4 PET scans and clinical assessments over 2 years. By the 2-year follow-up, 30 (32%) of 94 had progressed to MCI: 7 (7%) reverted to normal cognitive function and 57 (61%) remained MCI. Two (4.5%) of 44 healthy controls had progressed to MCI. All of the individuals with AD at baseline remained in that category. The proportion of patients with abnormal PET scores at baseline was 85% in the AD group, 40% in the MCI group, and 11% in the control group. An abnormal PET score at baseline had a sensitivity to predict disease progression of 0.57 and a specificity of 0.67. The area under the receiver-operating characteristic (ROC) curve was 0.75 for PET scores. Areas under the ROC curve for predicting disease progression for the outcome measures MMSE and the Alzheimer’s Disease Assessment Scale-Cognitive, were 0.66 and 0.68, respectively. Conclusions about the utility of using this PET score in clinical practice cannot be drawn from the Herholz study; additional research is needed that evaluates whether patient management decisions using the PET score results in improved health outcomes.

A 2012 meta-analysis (24) pooled 7 studies of FDG PET and 6 studies of PET with carbon-11 Pittsburgh Compound B (PIB) for prediction of conversion to AD among patients with MCI. Areas under the ROC curve were 0.88 for FDG PET and 0.85 for PIB PET. This report lacked comparisons with other means of predicting conversion from MCI to AD. It also lacks a discussion of how PET might influence treatment decisions and whether use of PET improves health outcomes. In 2014, these researchers published a Cochrane review addressing the same question. (25) Literature was searched through 2012, and 9 cohort studies of PIB-PET in patients with MCI were included (total N=274). Study quality was limited due to poor reporting. Across all trials, 112 patients (41%) converted to AD. Range of reported sensitivities and specificities was 83% to 100% and 46% to 88%, respectively. Because of heterogeneity across trials in the conduct of PIB-PET and in cutoffs used to indicate a positive test, meta-analysis was not done.

It should be noted that much of the present interest in detecting AD early is to develop and test treatments that might affect disease progression. This is clearly an important goal, but several important challenges must be overcome before PET imaging is used routinely in clinical practice to detect preclinical AD, so that treatment can be started. Additionally, other methods of diagnosing AD that do not involve imaging are also being explored.

Due to the lack of direct evidence that this imaging technique will result in a change in management that will improve patient outcomes, PET for AD and dementia is considered not medically necessary.

Vasculitis

In 2011, Treglia et al published a systematic review of PET and PET/CT in patients with large vessel vasculitits. (26) The investigators identified 32 studies with a total of 604 vacuities patients. The authors did not pool findings of the studies. They concluded that PET and PET/CT may be useful for initial diagnosis and assessment of severity of disease and that the role of these imaging methods in monitoring treatment response is unclear. They also concluded that “given the heterogeneity between studies with regard to PET analysis and diagnostic criteria, a standardization of the technique is needed.” The studies cited in support of using PET for diagnosing large vessel vasculitits had small sample sizes; 1 study included 25 vacuities patients and 44 controls; the others had total sample sizes of fewer than 20 patients.
Lehmann et al in Germany published a study after the Treglia review (2011). (27) PET scans of 20 patients with giant cell arthritis or Takayasu arthritis, and 20 healthy controls were retrospectively reviewed by 2 experienced nuclear medicine experts on a blinded basis. PET was found to have a sensitivity of 65% and a specificity of 80% for identifying patients with a diagnosis of large vessel vasculitis. The 2 reviewers agreed on the diagnosis in 34 (85%) of 40 of scans; the interrater agreement (Cohen's kappa) was 0.70. The authors concluded that, due to the low sensitivity and specificity, the diagnosis of large vessel vasculitis should not be based solely on PET findings. Study limitations included its retrospective study design and exclusion of individuals with suspected, rather than established, large vessel vasculitis.

The Lehmann study previously described was included in a 2014 systematic review of FDG-PET in giant cell arteritis. (28) A standardized method for assessing vascular inflammation based on the intensity of FDG uptake is currently lacking, and the investigators sought to compare the diagnostic performance of qualitative and semiquantitative methods. Of 19 included studies, 10 used qualitative FDG uptake criteria to characterize inflammation, 6 used semiquantitative criteria, and 3 (including the Lehmann study) used both. Overall, qualitative methods were more specific but less sensitive than semiquantitative methods. Diagnostic performance varied by vessel and by thresholds (cutoffs) for positivity. For qualitative methods, sensitivity and specificity were 56% to 77% and 77% to 100%, respectively; positive predictive value (PPV) and negative predictive value (NPV) were 93% to 100% and 70% to 82%, respectively. For semiquantitative methods, sensitivity and specificity were 58% to 90% and 42% to 95%, respectively; PPV and NPV were 79% to 89% and 95% to 98%, respectively. For mixed methods, sensitivity and specificity were 65% to 100% and 45% to 100%, respectively.

**Other Indications**

Review articles on the use of PET in patients with carotid stenosis (29); inflammatory diseases (30); fever of unknown origin (31, 32); hyperinsulinemic hypoglycemia (33, 34); spinal infections (35, 36); mycobacterium infection (37); Creutzfeldt–Jakob disease (38); vascular prosthetic graft infection (39); prosthetic infection after knee or hip arthroplasty (40); inflammatory bowel disease (41, 42); and multiple sclerosis (43) indicate insufficient evidence on the benefit of PET for these indications. Many of the studies cited in the reviews were small, retrospective, published in the 1990s to early 2000s, and/or many studies did not directly compare one modality with another in the same patient group or connect the PET results in individual patients to improved clinical outcomes.

A 2008 meta-analysis on using FDG-PET to diagnose prosthetic joint infection following hip or knee replacement reported pooled sensitivity and specificity of 82.1% (95% CI, 68.0% to 90.8%) and 86.6% (95% CI 79.7% to 91.4%), respectively. (44) The authors noted, however, that results should be interpreted with caution because of significant heterogeneity identified among the 11 studies included (which confers substantial uncertainty on the pooled estimates). Efforts to identify sources of heterogeneity were mostly unsuccessful; there were differences in performance based on location of prostheses (hip vs knee) and whether filtered back projection or iterative reconstruction was used. The authors stated that a large, multicenter trial is needed to evaluate the use of FDG-PET for identifying infection around joint prostheses. Both this study and a 2009 study on the same clinical issue found that the specificity of PET was significantly greater for hip prostheses than for knee prostheses. (45)
The articles noted that these results were based on the use of PET alone. CT is generally not useful in evaluating potential infections around joint prostheses because of the artifacts caused by the metallic implants, so additional research would be needed on combined PET/CT. The 2009 study compared the accuracy of PET with a triple-phase scan and with white blood cell imaging. The authors concluded that the latter is the most accurate but also the most complex and time-consuming modality, while the former is readily available and the easiest to perform. However, these comparisons are open to question because the methods were poorly described and the authors appeared to mix together results from single-arm studies on one modality with comparative studies.

A 2011 systematic review addressed use of PET in evaluating disease activity in patients with sarcoidosis (46). The report does not include quality assessment of individual studies, a critical feature of a well-conducted systematic review. Only 3 small studies out of 9 reviewed included data from a comparator imaging modality, thus conclusions about comparative diagnostic performance cannot be reached.

Balink et al (2014) in the Netherlands conducted a retrospective, multicenter study to assess the diagnostic accuracy of FDG-PET/CT for correctly diagnosing patients presenting with inflammation of unknown origin. (47) Eligible patients were afebrile (body temperature <100.9°F); had “prolonged and perplexing” inflammation, defined as clinical complaints accompanied by persistently elevated C-reactive protein and erythrocyte sedimentation rate; and were referred for FDG-PET/CT by an internist or rheumatologist. Of 140 enrolled patients, a final diagnosis was subsequently confirmed (by histopathology, microbiological assays, clinical and imaging follow-up, or response to treatment) in 104 (74%); final diagnosis was not based on FDG-PET/CT results. Most patients with no final diagnosis resolved spontaneously and were considered negative for disease for the purposes of this study. Sensitivity, specificity, PPV, and NPV of FDG-PET/CT was 91%, 83%, 94%, and 77%, respectively. Limitations of the study include selection bias due to the selection criteria and retrospective design, and nonstandard diagnostic workup, which may have affected final diagnoses and study results.

Ongoing and Unpublished Clinical Trials

A recent search of clinicaltrials.gov identified 2 phase 3 studies evaluating PET for miscellaneous applications.

- Metabolic Cerebral Imaging in Incipient Dementia (MCI-ID) (NCT00329706) is a randomized controlled trial evaluating whether PET scanning can distinguish between patients with early Alzheimer changes in their brains from patients with other types of cognitive impairment. All participants (estimated enrollment is 710) will undergo scanning with FDG-PET. Patients will be randomized to immediate release of the PET report or a 2-year delay in release of the report. Outcomes include change in cognitive function, utilization of health resources, and prescriptions for Alzheimer-specific therapies. The expected study completion date is January 2016.

- 18F-AV-133 PET will be used to differentiate Parkinson disease from other movement disorders in an open-label multicenter study (NCT01550484). The estimated enrollment for this study is 150 with an anticipated completion date of March 2016.
Practice Guidelines and Position Statements

American Academy of Neurology
Evidence-based practice parameters from the AAN are summarized in Table 1.

Table 1. AAN Practice Parameters on Diagnosis of Dementia

<table>
<thead>
<tr>
<th>Practice Parameter</th>
<th>Date</th>
<th>PET Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of dementia (48)</td>
<td>2001, r: 2004 (UIP)</td>
<td>PET imaging is not recommended for routine use in the diagnostic evaluation of dementia (LOR: moderate clinical certainty).</td>
</tr>
<tr>
<td>Early detection of dementia (49)</td>
<td>2001, r: 2003 (UIP)</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Diagnosis of dementia in PD (50)</td>
<td>2006, r: 2013</td>
<td>Evidence is insufficient to support or refute FDG-PET as a means of distinguishing PD from other parkinsonian syndromes.</td>
</tr>
<tr>
<td>Evaluation of depression, psychosis, and dementia in PD (51)</td>
<td>2006 (UIP)</td>
<td>Not addressed</td>
</tr>
</tbody>
</table>

LOR: level of recommendation; PD: Parkinson disease; r: reaffirmed; UIP: update in progress

American Academy of Orthopaedic Surgeons
AAOS published evidence-based, consensus guidelines in 2010.52 FDG-PET is considered “an option in patients in whom diagnosis of periprosthetic joint infection has not been established and are not scheduled for reoperation.” (Strength of recommendation: limited [quality of the supporting evidence is unconvincing, or well-conducted studies show little clear advantage of one approach over another])

American College of Radiology
Evidence- and consensus-based appropriateness criteria from ACR are summarized in Table 2.

Table 2. ACR Appropriateness Criteria for Miscellaneous Indications of FDA-PET/CT

<table>
<thead>
<tr>
<th>Appropriateness Criteria</th>
<th>Last Review Date</th>
<th>FDG-PET/CT Criteria</th>
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<tbody>
<tr>
<td>Dementia and movement disorders (53)</td>
<td>2014</td>
<td>May be appropriate in patients with possible or probable AD and to differentiate suspected FTD, LBD, CJD, or vascular dementia; usually not appropriate in patients with suspected HD, clinical features of PD or hemochromatosis, or motor neuron disease</td>
</tr>
<tr>
<td>Imaging after TKA (54)</td>
<td>2011</td>
<td>Usually not appropriate for routine follow-up of an asymptomatic patient, in the work-up for suspected periprosthetic infection, or for evaluation of prosthetic loosening</td>
</tr>
<tr>
<td>Seizures and epilepsy (55)</td>
<td>2014</td>
<td>Usually appropriate for surgical planning in medically refractory epilepsy; may be appropriate for new-onset seizure unrelated to trauma in adults (age ≥18 years) and for post-traumatic (subacute or chronic), new-onset seizure; otherwise, usually not appropriate for new-onset seizure</td>
</tr>
</tbody>
</table>
Infectious Diseases Society of America

IDSA published evidence-based, consensus guidelines on the diagnosis and management of prosthetic joint infections in 2013. (59) Guideline authors concluded that PET should not be routinely used to diagnoses prosthetic joint infection (Strength of recommendation: B [based on moderate evidence; Quality of evidence: III [expert opinion and descriptive studies]).

IDSA published evidence-based, consensus guidelines on the diagnosis and treatment of diabetic foot infections in 2012. (60) Guideline authors concluded that the role of FDG-PET in evaluating a diabetic foot infection has not been established.

U.S. Preventive Services Task Force Recommendations

Not applicable

Summary

Positron emission tomography (PET) for selected patients with epilepsy and patients with chronic osteomyelitis may be considered medically necessary.

There is insufficient evidence on the value of PET for other miscellaneous (non-cardiac, non-oncologic) indications. Studies are needed that demonstrate that PET will result in a change in management that will improve patient outcomes to determine that it is a clinically useful test. Therefore, for indications including those listed in the Policy section, PET is considered not medically necessary.

Medicare National Coverage

National Coverage Determination (NCD) for FDG-PET for Dementia and Neurodegenerative Diseases (220.6.13):

“Medicare covers FDG-PET scans for either the differential diagnosis of fronto-temporal dementia (FTD) and Alzheimer’s disease (AD) under specific requirements; OR, its use in a Centers for Medicare & Medicaid Services (CMS)-approved practical clinical trial focused on the utility of FDG-PET in the diagnosis or treatment of dementing neurodegenerative diseases”. Specific requirements for each indication are clarified in the document. (61)
National Coverage Determination (NCD) for FDG-PET for Infection and Inflammation (220.6.16)

"The CMS is continuing its national non-coverage of FDG-PET for the requested indications. Based upon our review, CMS has determined that the evidence is inadequate to conclude that FDG-PET for chronic osteomyelitis, infection of hip arthroplasty, and fever of unknown origin improves health outcomes in the Medicare populations, and therefore has determined that FDG-PET for chronic osteomyelitis, infection of hip arthroplasty, and fever of unknown origin is not reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act.” (62)

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398. |
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<th>Radiology</th>
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<td>Effective Date:</td>
<td>July 15, 2015</td>
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<tr>
<td>Subsection:</td>
<td>Miscellaneous (Non-cardiac, Non-oncologic) Applications of Positron Emission Tomography</td>
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Subject: Miscellaneous (Non-cardiac, Non-oncologic) Applications of Positron Emission Tomography

Policy History

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<tr>
<td>June 2012</td>
<td>New Policy</td>
<td>Policy updated with literature search; Sarcoidosis added as not medically necessary indication, no other changes to policy statement.</td>
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<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy update with literature review. Reference 12 added; no changes to policy statement.</td>
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<td>June 2014</td>
<td>Update Policy</td>
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Keywords

PET (Positron Emission Tomography), Miscellaneous Applications
Positron Emission Tomography (PET), Miscellaneous Applications
Positron Emission Transverse Tomography (PETT)
Tomography, Positron Emission, Miscellaneous Applications

This policy was approved by the FEP Pharmacy and Medical Policy Committee on June 19, 2015 and is effective July 15, 2015.

Signature on File

Deborah M. Smith, MD, MPH