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

Policy # 00104
Original Effective Date: 01/28/2002
Current Effective Date: 02/20/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Positron Emission Tomography (PET) Cardiac Applications are considered in medical policy 00103.

Note: Positron Emission Tomography (PET) Oncology Applications are considered in medical policy 00105.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider positron emission tomography (PET) using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) in the diagnosis of chronic osteomyelitis to be eligible for coverage.

Based on review of available data, the Company may consider positron emission tomography (PET) using FDG in the assessment of selected patients with epileptic seizures who are candidates for surgery to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for the use of positron emission tomography (PET) in the assessment of selected patients with epileptic seizures will be considered when the following criteria are met:

- Complex partial epileptic seizures that have failed to respond to medical therapy; and
- Resection of a suspected epileptogenic focus located in a region of the brain accessible to surgery has been recommended; and
- 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; and
- The purpose of the positron emission tomography (PET) examination should be to avoid subjecting the patient to extended preoperative electroencephalographic (EEG) recording with implanted electrodes or to help localize and minimize the number of sites for implanted electrodes to reduce the morbidity of that procedure.

When Services Are Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of positron emission tomography (PET) for all other miscellaneous indications, including but not limited to the following, to be investigational:*
Central Nervous System (CNS) diseases

- Autoimmune disorders with CNS manifestations, including:
  - Behçet’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’s 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
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- 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 syndrome

**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
Background/Overview

Positron emission tomography 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.

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.

Note: This policy only addresses the use of radiotracers detected with the use of dedicated full-ring PET scanners. Radiotracers such as 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.

FDA or Other Governmental Regulatory Approval

U.S. FDA

The 1997 FDA Modernization Act (FDAMA) 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).
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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 takes effect on December 12, 2011. More detailed information available online.

Centers for Medicare and Medicaid Services (CMS)
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 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.

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."

Rationale/Source
Policies on PET were originally based on 4 Technology Evaluation Center (TEC) Assessments that addressed various applications of PET. This evidence review has been updated regularly with literature reviews of the MEDLINE database, most recently for the period through July 23, 2015.

Epilepsy
A 2007 meta-analysis on the use of 2-[fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography (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 note, however, the difficulty of the analysis because of differences in study design 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).

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.

Chronic Osteomyelitis
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. A meta-analysis of 4 studies found sensitivity of 74% (95% confidence interval [CI], 60% to 85%), specificity of 91% (95% CI, 85% to 96%), positive likelihood ratio of 5.56 (95% CI, 2.02 to 15.27), negative likelihood ratio of 0.37 (95% CI, 0.10 to 1.35), and diagnostic odds ratio of 16.96 (95% CI, 2.06 to 139.66).The area under the summary receiver operating characteristic (ROC) curve was 0.874.
In 2005, Termaat and colleagues published a systematic review and meta-analysis of diagnostic imaging to assess chronic osteomyelitis. The authors reviewed studies on 6 imaging approaches to chronic osteomyelitis, including FDG-PET and concluded that PET is the most accurate mode (pooled sensitivity: 96% [95% CI: 88–99%]; pooled specificity: 91% [95% CI: 81–95%]) for diagnosing chronic osteomyelitis. Leukocyte scintigraphy was adequate in the peripheral skeleton (sensitivity: 84% [95% CI: 72–91%]; specificity: 80% [95% CI: 61–91%]) but was inferior in the axial skeleton (sensitivity: 21% [95% CI: 11–38%]; specificity: 60% [95% CI: 39–78%]). The assessment of PET was based on 4 prospective, European studies published between 1998 and 2003, with a total of 1,660 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”; 2) 22 trauma patients scheduled for surgery who had suspected metallic implant-associated infection; 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; and 4) 30 consecutive non-diabetic patients referred for possible chronic osteomyelitis. The results appeared to be robust across fairly diverse clinical populations, which strengthen the conclusions.

Alzheimer’s Disease and Dementia
A 2015 Cochrane Review intended to determine the diagnostic accuracy of FDG PET for detecting people with mild cognitive impairment (MCI) at baseline who would clinically convert to Alzheimer disease dementia or other forms of dementia at follow-up. Database searches were performed to January 2013. Included studies evaluated the diagnostic accuracy of FDG PET to determine the conversion from MCI to Alzheimer disease dementia or to other forms of dementia, including any or all of vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. Two blinded review authors independently extracted data, resolving disagreement by discussion, with the option to involve a third review author as arbiter if necessary. Fourteen studies with a total 421 participants were included in the analysis. The sensitivities for conversion from MCI to Alzheimer disease dementia were between 25% and 100%, while the specificities were between 15% and 100%. The summary receiver operating characteristic (ROC) curve estimated that the sensitivity was 76% (95% CI, 54 to 90) at the included study median specificity of 82%, equating a positive likelihood ratio of 4.03 (95% CI, 3 to 5), and a negative likelihood ratio of 0.34 (95% CI, 0.15 to 0.75). Three studies recruited participants from the same Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort but only the largest ADNI study (Herholz, 2011) is included in the meta-analysis. At the median specificity of 82%, the estimated sensitivity was between 74% and 76%. In addition to evaluating Alzheimer disease dementia, 5 studies evaluated the accuracy of FDG PET for all types of dementia. The sensitivities were between 46% and 95% while the specificities were between 29% and 100%; however, a meta-analysis was precluded because of too few studies with small numbers of participants. The report indicates most studies were poorly reported, and the majority of included studies had an unclear risk of bias, mainly for the reference standard and participant selection domains. According to the assessment of index test domain, more than 50% of studies were of poor methodological quality.

In a 2014 systematic review (quality assessment of included studies was not reported), Davison et al reported diagnostic performance of FDG-PET in 3 studies (total N=197) that used histopathology as reference standard. In patients with or without a clinical diagnosis of Alzheimer disease, 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
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Studies), sensitivity and specificity of SPECT were 63% to 87% and 73% to 90%, respectively. For predicting conversion from MCI to Alzheimer disease, 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.

In 2014, Zhang and colleagues published an update of a 2012 Cochrane review that addressed PET with carbon-11 Pittsburgh Compound B (PIB) for prediction of conversion to Alzheimer disease among patients with MCI. 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 Alzheimer disease. 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, data were not quantitatively pooled.

The prior 2012 meta-analysis by Zhang pooled 7 studies of FDG-PET and 6 studies of PET with carbon-11 Pittsburgh Compound B (PIB) for prediction of conversion to Alzheimer disease 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 Alzheimer disease. It also lacked a discussion of how PET might influence treatment decisions and whether use of PET improves health outcomes.

A 2009 meta-analysis compared the ability of FDG-PET, single-photon emission computed tomography (SPECT), and structural magnetic resonance imaging (MRI) to predict patients’ conversion from MCI to Alzheimer disease. 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.

A 2001 technology assessment conducted at Duke University through the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center used decision-analysis modeling to examine whether the use of FDG-PET would improve health outcomes when used for diagnosis of Alzheimer disease in 3 clinical populations: patients with dementia, patients with MCI, or subjects with no symptoms but with a first-degree relative with Alzheimer disease. PET was found to have 88% sensitivity (95% CI, 79% to 94%) and 87% specificity (95% CI, 77% to 93%) for diagnosing Alzheimer disease. 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 Alzheimer disease.

In 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 [Alzheimer disease] 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.” 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 MCI who were at greatest risk to progress to Alzheimer disease. Additionally, Medicare considered a consensus report by the Neuroimaging Work Group of the Alzheimer’s Association and proceedings of an expert panel discussion of neuroimaging in AD, convened by the National Institute of Aging and Medicare.

A 2011 prospective study by Herholz et al in the U.K. used a quantitative PET score previously devised by this research group to evaluate disease progression in MCI and Alzheimer disease; a software program was available to calculate the score. 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 patients with mild MCI 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 Alzheimer disease at baseline remained in that category. The proportion of patients with abnormal PET scores at baseline was 85% in the Alzheimer disease 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 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.

Durand-Martel et al noted in 2010 that the sensitivity of clinical diagnosis for Alzheimer disease varies between 75% and 98%, with an average of 82%. Therefore, comparing PET results with 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.

A 2008 multicenter, international study with 548 patients, including normal patients and those with MCI, Alzheimer disease, frontotemporal dementia, and dementia with Lewy bodies, used Neurological Statistical Image Analysis (Neurostat, University of Washington) to process the results. Excluding 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% Alzheimer disease, 92% dementia with Lewy bodies, and 94% frontotemporal dementia (p<0.001). PET patterns were also 98% sensitive and 92% specific (p<0.001) in distinguishing MCI from unimpaired patients.

Vasculitis
In 2015 a systematic review was published that aimed to clarify the role of FDG-PET in the management of large-vessel vasculitis (LVV), focusing on 3 issues: describe and determine the different FDG-PET criteria for the diagnosis of vascular inflammation; establish the performance of FDG-PET for the diagnosis of
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large-vessel inflammation in giant cell arteritis (GCA) patients; and, define the performance of FDG-PET to evaluate the disease inflammatory activity in patients with Takayasu arteritis (TA). The MEDLINE, Cochrane Library, and EMBASE databases were searched for articles that evaluated the value of FDG-PET in LVV, from January 2000 to December 2013. Inclusion criteria were American College of Rheumatology criteria for GCA or TA, definition of a PET positivity threshold, and more than 4 cases included. The sensitivity and specificity of FDG-PET for the diagnosis of large-vessel inflammation were calculated from each included individual study, and then pooled for meta-analysis with a random-effects model. Twenty-one studies (413 patients, 299 controls) were included in the systematic review. FDG-PET showed FDG vascular uptake in 70% (288/413) of patients and 7% (22/299) of controls. Only vascular uptake equal to or higher than the liver uptake was significantly different between GCA/TA patients and controls (p<0.001). The meta-analysis of GCA patients (4 studies, 57 patients) shows that FDG-PET has high sensitivity and specificity for the diagnosis of large-vessel inflammation in GCA patients in comparison to controls, with a pooled sensitivity of 90% (95% CI, 79% to 93%) and a pooled specificity of 98% (95% CI, 94% to 99%). The meta-analysis of TA patients (7 studies, 191 patients) shows that FDG-PET has a pooled sensitivity of 87% (95% CI, 78% to 93%) and specificity of 73% (95% CI, 63% to 81%) for the assessment of disease activity in TA, with up to 84% specificity in studies using National Institutes of Health criteria as the disease activity assessment scale. FDG-PET showed good performances in the diagnosis of large-vessel inflammation, with higher accuracy in GCA patients than in TA patients. Although a vascular uptake equal to or higher than the liver uptake appears to be a good criterion for the diagnosis of vascular inflammation, further studies are needed to define the threshold of significance as well as the clinical significance of the vascular uptake.

A 2014 systematic review included studies of FDG-PET in GCA. 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.

In 2011, Treglia et al published a systematic review of PET and PET/CT in patients with LVV. The investigators identified 32 studies with a total of 604 vasculitis 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 vasculitis had small sample sizes; 1 study included 25 vasculitis patients and 44 controls; the others had total sample sizes of fewer than 20 patients.
Another study published in 2011 reported results on PET scans of 20 patients with GCA or TA and 20 healthy controls that were retrospectively reviewed by 2 experienced nuclear medicine experts. PET was found to have a sensitivity of 65% and a specificity of 80% for identifying patients with a diagnosis of LVV. The 2 reviewers agreed on the diagnosis in 34 (85%) of 40 scans; intrarater agreement (Cohen's κ) was 0.70.

Other indications
Numerous review articles describe the use of PET in patients with carotid stenosis; inflammatory diseases; fever of unknown origin; hyperinsulinemic hypoglycemia; spinal infections; mycobacterium infection; Creutzfeldt-Jakob disease; vascular prosthetic graft infection; prosthetic infection after knee or hip arthroplasty; inflammatory bowel disease; and, multiple sclerosis. Many of the studies cited in the reviews were small, retrospective, and published in the 1990s to early 2000s; many studies did not directly compare 1 modality with another in the same patient group or connect the PET results in individual patients to improved clinical outcomes.

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

A 2008 meta-analysis of 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. The authors noted significant heterogeneity among the 11 studies included in the analysis. Differences in performance were based on location of prostheses (hip vs knee) and whether filtered back projection or iterative reconstruction was used. 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. The articles also 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.

A retrospective, multicenter study in 2014 assessed the diagnostic accuracy of FDG-PET/CT for correctly diagnosing patients presenting with inflammation of unknown origin. 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.
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Ongoing clinical trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT00329706</td>
<td>Early and Long-Term Value of Imaging Brain Metabolism</td>
<td>710</td>
<td>Jan 2016</td>
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<td>NCT01550484*</td>
<td>An Open Label, Multicenter Study, Evaluating the Safety and Efficacy of 18F-AV-133 PET Imaging to Identify Subjects With Dopaminergic Degeneration Among Subjects Presenting to a Movement Disorders Specialty Clinic With an Uncertain Diagnosis</td>
<td>150</td>
<td>Mar 2016</td>
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</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

Summary of Evidence

The evidence on FDG-PET for selected patients who have epilepsy who are candidates for surgery includes 2 meta-analyses. Relevant outcomes are symptoms, change in disease status, functional outcomes, health status measures, quality of life, hospitalizations, medication use, and resource utilization. One analysis shows FDG-PET had a predictive value for a good outcome of 86%, the other analysis suggested it was difficult to discern the incremental value of FDG-PET in patients who have foci well localized by ictal scalp electroencephalography and magnetic resonance imaging. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence on FDG-PET for diagnosis of patients who have suspected osteomyelitis includes 2 meta-analyses. Relevant outcomes are symptoms, change in disease status, functional outcomes, health status measures, quality of life, hospitalizations, medication use, and resource utilization. One systematic review and meta-analysis of 9 studies showed FDG-PET and FDG-PET/CT was found to be useful for diagnosis of suspected osteomyelitis in the foot of patients with diabetes. The results of the second meta-analysis showed FDG-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. The results appeared to be robust across fairly diverse clinical populations, which strengthen the conclusions. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence on FDG-PET for other miscellaneous (noncardiac, nononcologic) indications includes review articles and a few systematic reviews. Relevant outcomes are overall survival, symptoms, change in disease status, functional outcomes, health status measures, quality of life, hospitalizations, medication use, and resource utilization. Many of the studies cited in the reviews were small, retrospective, published in the 1990s to early 2000s; many studies did not directly compare 1 modality with another in the same patient group or connect the PET results in individual patients to improved clinical outcomes. Studies are needed that demonstrate FDG-PET will result in a change in management that will improve patient outcomes to
determine that it is a clinically useful test. The evidence is insufficient to determine the effect of the technology on health outcomes.

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07/20/2004  Medical Policy Committee review. Format revision. No substance change to policy.
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07/13/2005  Medical Director review
07/19/2005  Medical Policy Committee review
08/24/2005  Managed Care Advisory Council approval
07/07/2006  Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
09/06/2006  Medical Director review
09/20/2006  Medical Policy Committee approval. No changes to policy guidelines.
06/13/2007  Medical Director review
06/20/2007  Medical Policy Committee approval. Policy updated with literature search. Chronic osteomyelitis added as “may be considered medically necessary” and giant cell arteritis added as “investigational”.
07/02/2008  Medical Director review
07/16/2008  Medical Policy Committee approval. No change to coverage eligibility.
07/02/2009  Medical Director review
07/22/2009  Medical Policy Committee approval. No change to coverage eligibility.
01/01/2010  Coding Revision
07/01/2010  Medical Policy Committee approval
07/21/2010  Medical Policy Implementation Committee approval. Two additional dementia subtypes added to the investigational policy statement indications (frontotemporal dementia and dementia with Lewy Bodies).
07/07/2011  Medical Policy Committee approval
07/20/2011  Medical Policy Implementation Committee approval. Minor changes to policy statements (investigational indication for schizophrenia moved from dementias to psychiatric diseases and disorders; “vasculitis” added to investigational “other” category).
02/15/2012  Coding updated.
06/28/2012  Medical Policy Committee review
07/27/2012  Medical Policy Implementation Committee approval. Added (Non-cardiac, Non-oncologic)” to the policy title. Mycobacterium infection and inflammatory bowel disease added as investigational indications.
08/01/2013  Medical Policy Committee review
08/21/2013  Medical Policy Implementation Committee approval. Sarcoidosis added as an investigational indication.
08/07/2014  Medical Policy Committee review
08/20/2014  Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015  Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015  Medical Policy Committee review
11/16/2015  Medical Policy Implementation Committee approval. Vascular prosthetic graft infection, fever of unknown origin, and inflammation of unknown origin added as investigational indications. Assessment of cerebral blood flow in newborns revised but no other changes to policy statements.

Next Scheduled Review Date:  11/2016
Positron Emission Tomography (PET) Miscellaneous (Non-cardiac, Non-oncologic) Applications

Policy # 00104
Original Effective Date: 01/28/2002
Current Effective Date: 02/20/2016

Coding
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>78608, 78609, 78811, 78812, 78813, 78814, 78815, 78816</td>
</tr>
<tr>
<td>HCPCS</td>
<td>A9526, A9552, A9580, G0235</td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:
A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient’s illness, injury or disease; and
Positron Emission Tomography (PET) Miscellaneous (Non-cardiac, Non-oncologic) Applications

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C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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