Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorodeoxyglucose F 18 Positron Emission Tomography (FDG-PET)

Policy # 00104
Original Effective Date: 01/28/2002
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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 FDG-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
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- 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 syndrome

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

**Musculoskeletal diseases**
- Spondylodiscitis
- Joint replacement follow-up
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Other
- Giant cell arteritis
- Vasculitis
- Vascular prosthetic graft infection
- Inflammatory bowel disease
- Sarcoidosis
- Fever of unknown origin
- Inflammation of unknown origin

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.

Positron emission tomography scans are based on the use of positron emitting radionuclide tracers coupled to other molecules, such as glucose, ammonia, or water. The radionuclide tracers simultaneously emit 2 high-energy photons in opposite directions that can be simultaneously detected (referred to as coincidence detection) by a PET scanner, which comprises multiple stationary detectors that encircle the region of interest.

A variety of tracers are used for PET scanning, including oxygen 15, nitrogen 13, carbon 11, and fluorine 18 (F 18). The radiotracer most commonly used in oncology imaging has been F 18, coupled with deoxyglucose (FDG), which has a metabolism related to glucose metabolism. While FDG has traditionally been used in cancer imaging, it potentially has many other applications.

Epilepsy
Approximately one-third of patients with epilepsy do not achieve adequate seizure control with antiepileptic drugs. Individuals with intractable epilepsy are candidates for other treatments such as epilepsy surgery. Many effective surgical procedures are available and the treatment selected depends on characteristics of the seizures (eg, the epileptogenic zone) and the extent to which it can be resected safely. Neuroimaging techniques, such as magnetic resonance imaging (MRI), electroencephalography (EEG), PET, single-photon emission computed tomography (SPECT), electric (ESI) and magnetic source imaging (MSI), and magnetic resonance spectroscopy (MRS), have been used to locate the epileptic focus, thereby helping to guide the operative strategy. Some patients with epilepsy will have no identifiable MRI abnormality to help identify the focal region. PET, particularly using FDG, is a neuroimaging technique frequently used in patients being considered for surgery. FDG-PET produces an image of distribution of glucose uptake in the brain, presumably detecting focal areas of decreased metabolism. PET may be able to correctly identify the focus in patients with unclear or unremarkable MRI results or discordant MRI and EEG results that could reduce the need for invasive EEG. PET scanning may also help to predict which patients will have a favorable outcome following surgery. The Engel classification system is often used to describe the surgical
outcome: class I: seizure free or free of disabling seizures; class II: almost seizure free; class III: worthwhile improvement; and class IV: no worthwhile improvement.

**Suspected Chronic Osteomyelitis**
Diabetic foot infections cause substantial morbidity and are a frequent cause of lower-extremity amputations. Foot infections can spread to contiguous deep tissues including the bone. Diagnosis of osteomyelitis is challenging. The reference standard for diagnosis is examination of bacteria from a bone biopsy along with histologic findings of inflammation and osteonecrosis. In an open wound, another potential test for osteomyelitis is probe-to-bone test, which involves exploring the wound for palpable bone with a sterile blunt metal probe. Plain radiographs are often used as screening tests before biopsy but they tend to have low specificity especially in early infection. When radiographs are inconclusive, a more sophisticated imaging technique can be used. Both MRI and computed tomography have high sensitivity for diagnosis of osteomyelitis, but cannot be used in patients with metal hardware. FDG-PET has high resolution that should be an advantage for accurate localization of leukocyte accumulation and can be used when MRI is not possible or inconclusive. In addition, PET semiquantitative analysis could facilitate the differentiation of osteomyelitis from noninfectious conditions such as neuropathic joint.

**Suspected Alzheimer Disease**
Definitive diagnosis of Alzheimer disease (AD) requires histopathologic examination of brain tissue obtained by biopsy or autopsy. In practice, clinical criteria based on clinical examination, neurological and neuropsychological examinations, and interviews with informants (e.g., family members or caregivers) are used to diagnose AD by excluding other diseases that can cause similar symptoms, and to distinguish AD from other forms of dementia. There are currently no cures or preventive therapies for AD. Early diagnosis might facilitate early treatment of cognitive, behavioral, and psychiatric symptoms which could perhaps delay functional deficits and improve quality of life. Early diagnosis may be crucial in the future if other therapies become available to treat or slow progression of disease. FDG-PET can demonstrate reduction in glucose metabolism associated with dementia. These changes in metabolism are detectable years before the onset of clinical symptoms. The changes typically have a characteristic pattern of hypometabolism that could be useful not only in distinguishing AD from normal aging but also from other dementias, psychiatric disorders, and cerebrovascular diseases.

**Large Vessel Vasculitis**
Large vessel vasculitis causes granulomatous inflammation primarily of the aorta and its major branches. There are 2 major types of large vessel vasculitis: giant cell arteritis (GCA) and Takayasu arteritis (TA). Classification criteria for GCA and TA were developed by American College of Rheumatology in 1990. The definitions have since been refined by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides. Biopsy and angiography are considered the criterion standard techniques for diagnosis but they are invasive and detect changes that occur late in disease. In practice, the diagnosis is challenging because patients tend to have nonspecific symptoms such as fatigue, loss of appetite, weight loss, and low grade fever as well as nonspecific lab findings such as increased C-reactive protein or erythrocyte sedimentation rate. Misdiagnosis is common particularly in the early stages of disease. Unfortunately, late diagnosis can lead to serious aortic complications and death. Since activated
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Inflammatory cells accumulate glucose, FDG-PET may be able to detect and visualize early inflammation in vessel walls and facilitate early diagnosis thereby allowing treatment with glucocorticoids before irreversible arterial damage has occurred.

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 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 herein.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
In 1994, the \(^{18}\)F FDG radiotracer was originally approved by the FDA through the new drug application (NDA 20-306) process. The original indication was for “the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.” Added indications in 2000 were for “Assessment of glucose metabolism to assist in the evaluation of malignancy...” and “Assessment of patients with coronary artery disease and left ventricular dysfunction....” Many manufacturers have NDAs for fluorodeoxyglucose fluorine 18.

In September 2005, 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 2009, and took effect on December 2011. The final guidance document was issued in December 2012. All PET drug manufacturers and compounders are required to operate under an approved NDA or abbreviated NDA, or effective investigational new drug application, by December 12, 2015. More detailed information is available online.

Alternative radiotracers to fluorodeoxyglucose in identifying AD are under investigation. In particular, there is interest in amyloid PET tracers (see evidence review 6.01.55).

Centers for Medicare and Medicaid Services (CMS)
The CMS issued a decision memorandum in 2003 that did not support coverage of FDG-PET in AD because the evidence did not demonstrate its use for improved patient outcomes.

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.

The NCD for FDG-PET for Infection and Inflammation (220.6.16) states that:
"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**

**Epilepsy**

A 1996 TEC Assessment reviewed evidence on the use of PET in individuals with seizure disorders from 12 studies in which the results of PET scans were correlated with results of an appropriate reference standard test. The highest quality blinded study (N=143) reported that PET correctly localized the seizure focus in 60% of patients, incorrectly localized it in 6%, and was inconclusive in 34%. The TEC Assessment concluded that because localization can be improved with PET, selection of surgical candidates is improved and, therefore, PET for assessing patients who have medically refractory complex partial seizures and are potential candidates for surgery met TEC criteria. All other uses of PET for the management of seizure disorders did not meet the TEC criteria. Summaries of characteristics and results of several meta-analyses of FDG-PET published since that TEC Assessment for either presurgical planning of patients who are candidates for epilepsy surgery or prediction of surgical outcomes are shown in Tables 1 and 2 and are briefly described below.

**Table 1. PET in Epilepsy Systematic Review Characteristics**

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dates</th>
<th>Included Studies</th>
<th>N (Range)</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burneo (2015)</td>
<td>1946-2013</td>
<td>5</td>
<td>NR</td>
<td>OBS</td>
<td>Diagnostic/prognostic accuracy,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>clinical utility</td>
</tr>
<tr>
<td>Englot (2012)</td>
<td>1990-2010</td>
<td>21(^a)</td>
<td>1199 (13-253)(^a)</td>
<td>OBS</td>
<td>Prognostic accuracy</td>
</tr>
</tbody>
</table>

NR: not reported; OBS: observational; PET: positron emission tomography.

\(^a\) Total number of studies and participants included; unclear if all studies included PET as a predictor.

Jones et al published a systematic review of neuroimaging for surgical treatment of temporal lobe epilepsy in 2016. Inclusion criteria were systematic reviews, randomized controlled trials (RCTs), or observational studies (with >20 patients and at least 1-year follow-up) of neuroimaging in the surgical evaluation for temporal lobe epilepsy. The authors searched EMBASE, MEDLINE, and Cochrane from 1988 to 2014. Twenty-seven studies with 3163 patients were included in the review and 11 of these studies with 1358 patients (all observational designs) evaluated FDG-PET. Good surgical outcome was defined as Engel classes I and II. Meta-analysis was not performed. Results are summarized in Table 2.

A 2016 meta-analysis of prognostic factors for seizure outcomes in patients with MRI-negative temporal lobe epilepsy included a search of MEDLINE from 2000 to 2015. Eighteen studies (total N=391 patients)
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were included with a mean or median follow-up of more than 1 year; however, only 5 studies (sample sizes not given) were included in the PET analysis. Seizure freedom was defined as freedom from any type of seizure or an Engel class I seizure outcome. Odds ratios and corresponding 95% confidence intervals (CIs) were calculated to compare the pooled proportions of seizure freedom between the groups who had localization of hypometabolism in the resected lobe versus those who did not. Table 2 shows summary results.

In 2015, Burneo et al published a recommendation report for the Program in Evidence-based Care (PEBC) and the PET steering committee of Cancer Care Ontario, which was based on a systematic review of studies of diagnostic accuracy and clinical utility of FDG-PET in the presurgical evaluation of adult and pediatric patients with medically intractable epilepsy. The literature review included searches of the MEDLINE, EMBASE, and OVID databases from the years 1946 to 2013, society meeting abstracts, practice guidelines, and the Cochrane database. Systematic reviews, RCTs, and observational studies that evaluated the use of FDG-PET in medically intractable epilepsy were eligible for inclusion. The reviewers included 39 observational studies (total N=2650 participants) in the qualitative review. Good surgical outcome was defined as Engel class I, II, or III, seizure-free, or significant improvement (<10 seizures per year and at least a 90% reduction in seizures from the preoperative year). Due to heterogeneity in patient populations, study designs, outcome measurements, and methods of PET interpretation, pooled estimates were not provided but ranges are shown in Table 2.

A 2012 meta-analysis on predictors of long-term seizure freedom after surgery for frontal lobe epilepsy included articles, found through a MEDLINE search for years 1990 through 2010, that had at least 10 participants and 48 months of follow-up. Long-term seizure freedom was defined as Engel class I outcome. Twenty-one studies (total N=1199 patients) were included; the number of studies that specifically addressed PET was not specified. Results are summarized in Table 2. The reviewers found that PET findings did not predict seizure freedom.

A 2007 meta-analysis on the use of FDG-PET for preoperative evaluation of adults with temporal lobe epilepsy included 46 studies published between 1992 and 2006 and identified through MEDLINE. Follow-up ranged from 3 to 144 months. Engel class I and II were defined as a good surgical outcome. The prognostic positive predictive value for ipsilateral PET hypometabolism was calculated but the reviewers noted significant variation in study designs and lack of precise data. They found that ipsilateral PET hypometabolism had a predictive value for a good outcome of 86% (see Table 2). The incremental value of PET was unclear. PET may not add value for patients well-localized by ictal scalp electroencephalography and MRI.

<table>
<thead>
<tr>
<th>Study</th>
<th>Included Studies</th>
<th>N (Range)</th>
<th>Outcome</th>
<th>Estimate</th>
<th>95% CI</th>
<th>( I^2 )</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones (2016)</td>
<td>11</td>
<td>1358</td>
<td>Surgical outcome</td>
<td>No overall summary given</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reported conflicting findings on prognostic importance of PET-identified focal hypometabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>NR</th>
<th>Surgical outcome (freedom from seizures)</th>
<th>OR for PET hypometabolism positive vs negative</th>
<th>Range</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang (2016)</td>
<td>5</td>
<td>NR</td>
<td></td>
<td>OR = 2.11 (95% CI, 0.95 to 4.65)</td>
<td>No pooling</td>
<td></td>
</tr>
<tr>
<td>Burneo (2015)</td>
<td>8</td>
<td>310</td>
<td>Percent agreement, localization with PET vs EEG</td>
<td>Range: 56%-90% overall (adults) 63%-90% in temporal lobe epilepsy (adults)</td>
<td>No pooling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>1064</td>
<td>Surgical prognostic accuracy (good surgical outcome)</td>
<td>Range: 96%-90% (adults)</td>
<td>No pooling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>690</td>
<td>Clinical decisions (influence decision making)</td>
<td>Range: 53%-71% (adults) 51%-95% (children)</td>
<td>No pooling</td>
<td></td>
</tr>
<tr>
<td>Englot (2012)</td>
<td>21*</td>
<td>1199*</td>
<td>Surgical prognostic accuracy (good surgical outcome)</td>
<td>% for PET focal vs PET nonlocal, 52% vs 48%</td>
<td>NR NR 0.61</td>
<td></td>
</tr>
<tr>
<td>Willmann (2007)</td>
<td>46</td>
<td>1112</td>
<td>Surgical prognostic accuracy (good surgical outcome)</td>
<td>PPV = 86%</td>
<td>NR NR NR</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; EEG: electroencephalography; NR: not reported; OR: odds ratio; PET: positron emission tomography; PPV: positive predictive value.

* Total number of studies and participants included; unclear if all studies included PET as a predictor.

Section Summary
The TEC Assessment and PEBC recommendations summarized evidence on the use of PET to localize seizure foci for presurgical evaluation. Although data were exclusively from observational studies and results heterogeneous, the findings generally supported the use of PET for presurgical evaluation of adult and pediatric patients with intractable epilepsy to localize foci. For predicting which patients would have a favorable surgery outcome, the data on PET were mixed but supported a possible moderate relation between PET findings and prognosis. Only observational studies are available, most having small sample sizes with varying patient characteristics and definitions of good surgical outcomes.

Suspected Chronic Osteomyelitis
In a 2013 systematic review of 9 studies (total N=299 patients), FDG-PET and PET with computed tomography (CT) were 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% 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 summary area under the receiver operating characteristic curve (AUC ROC) was 0.874.

In 2005, Termaat et al published a systematic review and meta-analysis of diagnostic imaging to assess chronic osteomyelitis. They 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% 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”; (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 nondiabetic patients referred for possible chronic osteomyelitis. The results appeared to be robust across fairly diverse clinical populations, which strengthen the conclusions.

Suspected Alzheimer Disease
This policy does not discuss PET tracers that bind to amyloid beta plaques. Summaries of characteristics and results of several meta-analyses of early diagnosis of AD in people with cognitive impairment or for differentiating between potential causes of dementia are shown in Tables 3 and 4 and are briefly described below.

Table 3. PET in Alzheimer Disease and Dementia Systematic Review Characteristics

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dates</th>
<th>Included Studies</th>
<th>N (Range)</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallagic (2015)</td>
<td>1999-2013</td>
<td>16</td>
<td>697 (19-94)</td>
<td>OBS</td>
<td>Diagnostic accuracy for predicting conversion to AD in those with MCI</td>
</tr>
<tr>
<td>Davison (2014)</td>
<td>Up to 2013</td>
<td>8</td>
<td>197 (7-199)</td>
<td>OBS</td>
<td>Diagnostic accuracy for diagnosis of AD, differential diagnosis in dementia, predicting conversion from MCI to AD</td>
</tr>
<tr>
<td>Bloudek (2011)</td>
<td>1990-2010</td>
<td>119</td>
<td>NR</td>
<td>OBS</td>
<td>Diagnostic accuracy for diagnosis of AD, differential diagnosis in dementia</td>
</tr>
<tr>
<td>Yuan (2009)</td>
<td>2001-2005</td>
<td>6</td>
<td>280 (17-128)</td>
<td>OBS</td>
<td>Diagnostic accuracy for predicting conversion to AD in those with MCI</td>
</tr>
</tbody>
</table>

AD: Alzheimer disease; AHRQ: Agency for Healthcare Research and Quality; MCI: mild cognitive impairment; NR: not reported; OBS: observational; PET: positron emission tomography.

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 AD 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 AD or to other forms of dementia. Sixteen studies (total N=697 participants) were included in the qualitative review and 14 studies (n=421 participants) were included in the analysis. Because there are no accepted thresholds to define PET positivity and studies used mixed thresholds for diagnosis, the reviewers used a hierarchical summary ROC to derived pooled estimates of performance characteristics at fixed values. Results are shown in Table 4.
Five 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 review indicated that most studies were poorly reported, and the majority of selected studies had an unclear risk of bias, mainly for the reference standard and participant selection domains.

In a 2014 systematic review (quality assessment of included studies was not reported), Davison et al reported studies on the diagnostic performance of FDG-PET and SPECT identified through a MEDLINE search up to February 2013. Three studies (197 patients) used histopathology as reference standard. 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 patients undergoing evaluation for dementia, sensitivity was 94% and specificity was 73%. Precision estimates were not given. In 3 different studies (271 participants), the sensitivities and specificities of FDG-PET for distinguishing AD from Lewy body dementia ranged from 83% to 99% and from 71% to 93%, respectively. And in 2 studies (183 participants), for predicting conversion from MCI to AD, sensitivity and specificity of PET were 82% and 57% versus 78% and 67%, respectively.

Bloudek et al (2011) published a meta-analysis of diagnostic strategies for AD. The authors included 119 studies of diagnostic performance characteristics published from 1990 to 2010. Studies were identified through a search of MEDLINE and included imaging, biomarkers, and clinical diagnostic strategies. Twenty studies included performance characteristics of FDG-PET for diagnosing AD compared to normal, nondemented controls. Thirteen studies described characteristics of FDG-PET for diagnosing AD compared to demented controls. FDG-PET demonstrated the highest area under the ROC curve, sensitivity, and specificity among all of the diagnostic methods for distinguishing AD from normal controls but had almost the lowest ROC comparing AD to non-AD demented controls (excluding MCI) due primarily to the low specificity in this group. Results are shown in Table 4.

A 2009 meta-analysis compared the ability of FDG-PET, SPECT, and structural MRI to predict patients' conversion from MCI to AD. Using 24 articles (total N=1112 patients) identified among from studies published between 1990 to April 2008 (6 studies with 280 patients 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. Results are shown in Table 4. There was strong evidence of between-study heterogeneity and marked asymmetry in the funnel plot (with studies missing from the bottom left quadrant), indicating possible publication bias of studies with null 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.

A 2001 technology assessment conducted for the Agency for Healthcare Research and Quality (AHRQ) used decision-analysis modeling to examine whether the use of FDG-PET would improve health outcomes for diagnosis of AD in 3 clinical populations: patients with dementia, patients with MCI, and subjects with no symptoms but with a first-degree relative with AD. For the review, a search was performed using MEDLINE, CINAHL, and the HealthSTAR databases from January 1995 to January 2001. Eighteen articles (total
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N=1018 participants) were included. Reference standard used in the studies was either histopathology or clinical diagnosis. Studies reported various cutoffs for PET positivity so an unweighted summary ROC method was used to calculate the pooled AUC. Results are summarized in Table 4. The reviewers concluded that outcomes for all 3 groups were better if all patients were treated with agents such as cholinesterase inhibitors rather than 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.

In 2004, the CMS 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 updated 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 AD. Additionally, CMS 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.

Section Summary
There are several systematic reviews of evidence on FDG-PET for diagnosing AD in people with cognitive impairment and for differentiating between AD and other dementias. Studies included in these reviews were generally of poor quality. There is no standard cutoff for PET positivity for diagnosing AD and many studies did not include postmortem confirmation of AD as the reference standard. These limitations lead to uncertainty about estimates of performance characteristics. Although it appears that FDG-PET has high sensitivity and specificity, the evidence does not compare the performance characteristics of clinical diagnosis with PET to clinical diagnosis without PET, so the incremental value of adding PET to the standard clinical diagnosis is unclear. No studies reported on clinical outcomes of patients diagnosed with versus without FDG-PET.

Table 4. PET in Alzheimer Disease and Dementia Systematic Review Outcome Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Included Studies</th>
<th>N</th>
<th>Outcome</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
</table>
| Smallagic (2015) | 14              | 421| Diagnostic accuracy               | • Sensitivity range: 25%-100%  
• Specificity range: 15%-100%  
• Pooled ROC (at median specificity), sensitivity: 76% (54% to 90%)  
• PLR: 4.03 (2.97 to 5.47)  
• NLR: 0.34 (0.15 to 0.75) |
| Davison (2014)   | 3               | 197| Diagnostic accuracy, overall     | • Sensitivity: 84%  
• Specificity: 74% |
|                | 2               | 183| Diagnostic accuracy, predicting conversion from | • Sensitivity range: 82%-57%  
• Specificity range: 78%-67% |
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<table>
<thead>
<tr>
<th>MCI to AD</th>
<th>Diagnostic accuracy, differentiating AD and LBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>292</td>
</tr>
</tbody>
</table>

Bloudek (2011) 20 NR Diagnostic accuracy, overall

<table>
<thead>
<tr>
<th>MCI to AD</th>
<th>Diagnostic accuracy, AD versus other dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>NR</td>
</tr>
</tbody>
</table>

Yuan (2009) 6 280 Diagnostic accuracy

<table>
<thead>
<tr>
<th>MCI to AD</th>
<th>Diagnostic accuracy, pooled ROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>729</td>
</tr>
</tbody>
</table>

Matchar (2001) 3 289 Diagnostic accuracy, distinguishing AD from non-AD dementia

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dates</th>
<th>Included Studies N (Range)</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee (2015)</td>
<td>Up to 2015 2000-2013</td>
<td>8 400 (21-93)</td>
<td>OBS</td>
<td>Diagnostic accuracy for GCA and TA</td>
</tr>
<tr>
<td>Puppo (2014)</td>
<td>1999-2014</td>
<td>19 977 (8-304)</td>
<td>OBS</td>
<td>Diagnostic accuracy for GCA (qualitative vs semiquantitative criteria)</td>
</tr>
<tr>
<td>Treglia (2011)</td>
<td>Up to 2011</td>
<td>14 604</td>
<td>OBS</td>
<td>Diagnostic accuracy for GCA; assessment of disease activity; monitor treatment response</td>
</tr>
<tr>
<td>Besson (2011)</td>
<td>Up to 2011</td>
<td>Unclear</td>
<td>OBS</td>
<td>Diagnostic accuracy for GCA</td>
</tr>
</tbody>
</table>

GCA: giant cell arteritis; OBS: observational; PET: positron emission tomography; PLR: positive likelihood ratio; ROC: receiver operating characteristic.

Suspected Large Vessel Vasculitis

Summaries of characteristics and results of several meta-analyses of FDG-PET that have been published on the diagnosis and management of large vessel vasculitis (LVV) are shown in Tables 5 and 6 and are briefly described below.

Table 5. PET in Large Vessel Vasculitis Systematic Review Characteristics

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dates</th>
<th>Included Studies</th>
<th>N (Range)</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee (2015)</td>
<td>Up to 2015 2000-2013</td>
<td>8 400 (21-93)</td>
<td>OBS</td>
<td>Diagnostic accuracy for GCA and TA</td>
<td></td>
</tr>
<tr>
<td>Puppo (2014)</td>
<td>1999-2014</td>
<td>19 977 (8-304)</td>
<td>OBS</td>
<td>Diagnostic accuracy for GCA (qualitative vs semiquantitative criteria)</td>
<td></td>
</tr>
<tr>
<td>Treglia (2011)</td>
<td>Up to 2011</td>
<td>14 604</td>
<td>OBS</td>
<td>Diagnostic accuracy for GCA; assessment of disease activity; monitor treatment response</td>
<td></td>
</tr>
<tr>
<td>Besson (2011)</td>
<td>Up to 2011</td>
<td>Unclear</td>
<td>OBS</td>
<td>Diagnostic accuracy for GCA</td>
<td></td>
</tr>
</tbody>
</table>

Lee et al (2015) performed a meta-analysis of the diagnostic accuracy of FDG PET or PET/CT for LVV. The search included studies indexed in PubMed, EMBASE, or Cochrane Library and published before February 2015 that used American College of Rheumatology (ACR) classification as the reference standard diagnosis. Eight studies were (total N=400 participants). Five studies included participants with both giant cell arteritis (GCA) and Takayasu arteritis (TA) while 3 included only GCA. Five studies evaluated FDG-PET and 3 evaluated FDG-PET/CT. Pooled estimates of sensitivity, specificity, positive likelihood ratio, and
negative likelihood ratio were calculated using a random-effects model and are shown in table 6. Interpretation of these results is limited by the use of ACR as the reference standard and the varying levels of disease activity in selected studies.

In 2015 a literature review on the role of FDG-PET in the management of LVV, focused on 3 issues: determining the different FDG-PET criteria for the diagnosis of vascular inflammation; establishing the performance of FDG-PET for the diagnosis of large-vessel inflammation in GCA patients; and defining the performance of FDG-PET to evaluate the disease inflammatory activity in patients with 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 ACR 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 selected study, and then pooled for meta-analysis with a random-effects model. Disease activity was assessed with the National Institutes of Health Stroke Scale or another activity assessment scale. 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 differed significantly between GCA plus TA patients and controls (p<0.001). A summary of the results is shown in Table 6. FDG-PET showed good performances in the diagnosis of large-vessel inflammation, with higher accuracy for diagnosing GCA patients than for detecting activity 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 comparing the diagnostic performance of qualitative and semiquantitative methods of FDG-PET interpretation. The review selected 19 studies (442 cases, 535 controls) found in PubMed or Cochrane Library through April 2014. The included studies had various reference standards. Ten used qualitative FDG uptake criteria to characterize inflammation, 6 used semiquantitative criteria, and 3 used both. Meta-analyses were not performed. Overall, qualitative methods were more specific, but less sensitive, than semiquantitative methods. Diagnostic performance varied by vessel and by thresholds (cutoffs) for positivity. Results are shown in Table 6.

In 2011, Treglia et al published a systematic review of PET and PET/CT in patients with LVV. The reviewers searched MEDLINE and Scopus for publications through April 2011 on the role of FDG-PET in LVV. They identified 32 studies (total N=604 vasculitis patients). Selected publications related to diagnosis, assessment of disease activity, extent of disease, response to therapy, and prediction of relapse or complications. The reviewers did not pool findings. They concluded that: (1) PET and PET/CT may be useful for initial diagnosis and assessment of severity of disease; (2) appeared to be superior to MRI in the diagnosis of LVV, but not in assessing disease activity under immunosuppressive treatment, in predicting relapse, or in evaluating vascular complications; (3) 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 LVV had small sample sizes.
Besson et al (2011) published a systematic review and meta-analysis of FDG-PET in GCA based on a search of MEDLINE, EMBASE, and the Cochrane Library up to November 2011. Studies were included if they evaluated the performance of FDG-PET for the diagnosis of GCA, had at least 8 participants, used ACR criteria as the reference standard to confirm diagnosis of GCA, and included a control group. Fourteen studies were selected; the number of participants in those studies was unclear. Six studies with 283 participants (101 vasculitis, 182 controls) were included in a meta-analysis. The meta-analysis calculated pooled estimates of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio, and diagnostic accuracy using a random-effects model. Results are shown in Table 6. There was statistically significant between-study heterogeneity for sensitivity, PPV, and NPV. All studies in the meta-analysis were small case-control studies.

### Table 6. PET in Large Vessel Vasculitis Systematic Review Outcome Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Included Studies</th>
<th>N</th>
<th>Outcome</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee (2015)</td>
<td>8</td>
<td>400</td>
<td>Diagnostic accuracy of PET and PET/CT for GCA and TA</td>
<td>Sensitivity: 76% (68% to 82%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Specificity: 93% (89% to 96%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PLR: 7.27 (3.71 to 14.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NLR: 0.30 (0.23 to 0.40)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>133</td>
<td>Diagnostic accuracy of PET and PET/CT for GCA</td>
<td>Sensitivity: 83% (72% to 91%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Specificity: 90% (80% to 96%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PLR: 7.11 (2.91 to 17.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NLR: 0.20 (0.11 to 0.34)</td>
</tr>
<tr>
<td>Soussan (2015)</td>
<td>4</td>
<td>233</td>
<td>Diagnostic accuracy for GCA</td>
<td>Sensitivity: 89.5% (78.5% to 96.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Specificity: 97.7% (CI, 94% to 99%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PLR: 28.7 (11.5; 71.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NLR: 0.15 (0.07; 0.29)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>237</td>
<td>Diagnostic accuracy for disease activity in TA</td>
<td>Sensitivity: 87% (78% to 93%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Specificity: 73% (63% to 81%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PLR: 4.2 (1.5; 12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NLR: 0.2 (0.1; 0.5)</td>
</tr>
<tr>
<td>Puppo (2014)</td>
<td>10</td>
<td>633</td>
<td>Diagnostic accuracy for GCA using qualitative criteria</td>
<td>Sensitivity range: 56%-77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Specificity range: 77%-100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PPV: 93% to 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NPV: 70% to 82%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>282</td>
<td>Diagnostic accuracy for GCA using semiquantitative criteria</td>
<td>Sensitivity range: 58%-90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Specificity range: 42%-95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PPV: 79% to 89%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>NPV: 95% to 98%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>72</td>
<td>Diagnostic accuracy for GCA using mixed qualitative and semiquantitative criteria</td>
<td>Sensitivity range: 65%-100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Specificity range: 45%-100%</td>
</tr>
<tr>
<td>Treglia (2011)</td>
<td>32</td>
<td>604</td>
<td>Diagnostic accuracy for GCA and TA; assessment of disease activity; monitor treatment response</td>
<td>No pooling; concluded that FDG-PET is useful “in the initial diagnosis and in the assessment of activity and extent of”</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Besson (2011)</th>
<th>6</th>
<th>283</th>
<th>Diagnostic accuracy for GCA</th>
</tr>
</thead>
</table>

- **Sensitivity**: 80% (63% to 91%)
- **Specificity**: 89% (78% to 94%)
- **PPV**: 85% (62% to 95%)
- **NPV**: 88% (72% to 95%)
- **PLR**: 6.73 (3.55 to 12.77)
- **NLR**: 0.25 (0.13 to 0.46)
- **Accuracy**: 84% (76% to 90%)

CI: confidence interval; CT: computed tomography; FDG: fluorodeoxyglucose; GCA: giant cell arteritis; LVV: large vessel vasculitis; NLR: negative likelihood ratio; NPV: negative predictive value; PET: positron emission tomography; PLR: positive likelihood ratio; PPV: positive predictive value; TA: Takayasu arteritis.

**Section Summary**

There have been several systematic review of diagnosis and management of LVV using FDG-PET. Most studies selected were small, many lacked controls and results were heterogeneous. Studies comparing PET to the true reference standard (biopsy or angiography) were rare. There are no consensus criteria to define the presence of vascular inflammation by FDG-PET in LVV and different parameters with visual and semiquantitative methods have been reported. Studies demonstrating changes in management based on PET results or improvements in clinical outcomes are lacking.

**Diverse Noncardiac or Nononcologic Conditions**

Numerous systematic reviews have described 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 Huntington disease. Many studies cited in these reviews were small, retrospective, and lacked standard definitions of PET interpretation and positivity; many 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. It did not include a 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 the location of prostheses (hip vs knee) and whether filtered back projection or iterative reconstruction was used. This meta-analysis 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.

**Ongoing clinical trials**

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

<table>
<thead>
<tr>
<th>Table 7. Summary of Key Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCT No.</strong></td>
</tr>
<tr>
<td>Ongoing</td>
</tr>
<tr>
<td>NCT00329706</td>
</tr>
<tr>
<td>NCT02084147</td>
</tr>
<tr>
<td>Unpublished</td>
</tr>
<tr>
<td>NCT01550484</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

**Summary of Evidence**

For individuals who have epileptic seizures who are candidates for surgery who have FDG-PET, the evidence includes 5 systematic reviews since the publication of 3 TEC Assessments. Relevant outcomes are symptoms, change in disease status, functional outcomes, health status measures, quality of life, hospitalizations, medication use, and resource utilization. The TEC Assessment and Program in Evidence-based Care PET recommendation report both concluded that FDG-PET accurately localizes the seizure focus compared to appropriate reference standards. A recent systematic review 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 on whether FDG-PET has a predictive value for a good surgical outcome is mixed. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected osteomyelitis who receive FDG-PET, the evidence includes 2 meta-analyses. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, functional outcomes, quality of life, and hospitalizations. One systematic review and meta-analysis of 9 studies showed FDG-PET and FDG-PET plus CT were useful for diagnosing 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 appear 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.
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For individuals who have suspected AD who receive FDG-PET, the evidence includes 5 systematic reviews of observational studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, quality of life, and hospitalizations. The studies included in the reviews were generally of poor quality. There is no standard cutoff for PET positivity for diagnosing AD and many studies have not included postmortem confirmation of AD as the reference standard, leading to uncertainty about estimates of performance characteristics. FDG-PET may have high sensitivity and specificity for diagnosing AD, but there is little evidence comparing the performance characteristics of clinical diagnosis with PET to clinical diagnosis without PET, so the incremental value of adding PET to the standard clinical diagnosis is unclear. No studies have reported on clinical outcomes of patients diagnosed with versus those without FDG-PET. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected large vessel vasculitis who receive FDG-PET, the evidence includes 5 systematic reviews of observational studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, morbid events, quality of life, hospitalizations, and treatment-related morbidity. Most studies included in the reviews were small and lacked controls. The reported performance characteristics were heterogeneous, but reviewers were unable to determine the source of heterogeneity. Studies comparing PET to the true reference standard of biopsy or angiography were rare. There are no consensus criteria to define the presence of vascular inflammation by FDG-PET in large vessel vasculitis, and different parameters with visual and semiquantitative methods have been reported. Studies demonstrating changes in management based on PET results or improvements in clinical outcomes are lacking. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have diverse noncardiac or nononcologic conditions (eg, central nervous system, pulmonary, and musculoskeletal diseases) who receive FDG-PET, the evidence includes 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 studies cited in the reviews were small, retrospective, and published in the 1990s to early 2000s; many 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 results will change management that improves 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.

References
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- 12/06/2001 Medical Policy Committee review
- 01/28/2002 Managed Care Advisory Council approval
- 06/24/2002 Format revision. No substance change to policy.
- 07/06/2004 Medical Director review
- 07/20/2004 Medical Policy Committee review. Format revision. No substance change to policy.
- 07/26/2004 Managed Care Advisory Council approval
- 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
Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorodeoxyglucose F 18 Positron Emission Tomography (FDG-PET)

Policy # 00104
Original Effective Date: 01/28/2002
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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
12/01/2016 Medical Policy Committee review
12/21/2016 Medical Policy Implementation Committee approval. Title change, added “FDG” to investigational statement. Updated background, rationale and references.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

Next Scheduled Review Date: 12/2017

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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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, C9461, G0235</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>
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*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
   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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