Medical Policy

***Current Policy Effective Date: 7/1/23**
(See policy history boxes for previous effective dates)

Title: Positron Emission Tomography (PET) for Miscellaneous Applications (Non-Cardiac, Non-Oncologic)

Description/Background

POSITRON EMISSION TOMOGRAPHY
Positron emission tomography (PET) scans couple positron emitting radionuclide tracers to other molecules, such as glucose, ammonia, or water. The radionuclide tracers simultaneously emit two 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. The radiotracer most commonly used in oncology imaging has been fluorine 18, coupled with fluorodeoxyglucose (FDG), which has a metabolism related to glucose metabolism. While FDG has traditionally been used in cancer imaging, it potentially has many other applications.

Regulatory Status

Following the U.S. Food and Drug Administration's (FDA) approval of the Penn-PET in 1989, a number of PET scan platforms have been cleared by FDA through the 510(k) process. These systems are intended to aid in detecting, localizing, diagnosing, staging and restaging of lesions, tumors, disease and organ function for the evaluation of diseases, and disorders such as, but not limited to, cardiovascular disease, neurologic disorders, and cancer. The images produced by the system can aid in radiotherapy treatment planning and interventional radiology procedures.

PET radiopharmaceuticals have been evaluated and approved as drugs by FDA for use as diagnostic imaging agents. These radiopharmaceuticals are approved for specific conditions.

In December 2009, FDA issued guidance for Current Good Manufacturing Practice for PET drug manufacturers (1) and, in August 2011, issued similar Current Good Manufacturing Practice guidance for small businesses compounding radiopharmaceuticals.(16) An additional final guidance document, issued in December 2012, required all PET drug manufacturers and compounders to operate under an approved new drug application (NDA) or abbreviated NDA, or investigational new drug application, by December 12, 2015.(3)

In 1994, the FDG radiotracer was originally approved by the U.S. Food and Drug Administration (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…."

Multiple manufacturers have approved NDAs for FDG.(4)

Medical Policy Statement

The safety and effectiveness of positron emission tomography (PET) scanning have been established. It is a useful diagnostic option for patients meeting patient selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Positron emission tomography (PET) using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) may be considered established when one of the following are met:

- The assessment of select patients with epileptic seizures who are candidates for surgery**
- The diagnosis of chronic osteomyelitis
- One time evaluation to differentiate between frontotemporal dementia and Alzheimer's disease when substantial diagnostic uncertainty remains after **ALL** of the following have been completed
  - Neuropsychological testing
  - Evaluation by a physician experienced in neurodegenerative disease
  - Structural imaging (CT or MRI)

**see policy guidelines below for clarification of surgery candidate

Exclusions:
The use of FDG-PET is experimental/investigational for all other miscellaneous indications, not listed in inclusion criteria above including, but not limited to:

CNS diseases

- Autoimmune disorders with CNS manifestations, including:
  - Behçet 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 ataxia
  - Olivopontocerebellar atrophy
  - Parkinson's disease
  - Progressive Supranuclear Palsy
  - Shy-Drager syndrome
  - Spinocerebellar Degeneration
  - Steele-Richardson-Olszewski disease
  - Tourette syndrome
- Dementias, including
  - Alzheimer disease
  - Multi-infarct dementia
  - Pick disease
  - Dementia with Lewy-Bodies
  - Presenile dementia
- Demyelinating diseases, such as multiple sclerosis
- Developmental, congenital, or inherited disorders, including:
  - Adrenoleukodystrophy
  - Down syndrome
  - Huntington chorea
  - Kinky-hair disease (Menkes' syndrome)
  - Sturge-Weber syndrome (encephalofacial angiomatosis) and the phakomatoses
- Miscellaneous
  - Chronic fatigue syndrome
  - Sick building syndrome
  - Post-traumatic stress disorder
- Nutritional or metabolic diseases and disorders, including:
  - Acanthocytosis
  - Hepatic encephalopathy
  - Hepatolenticular degeneration
  - Metachromatic leukodystrophy
  - Mitochondrial disease
  - Subacute necrotizing encephalomyelopathy
- Psychiatric diseases and disorders, including:
  - Affective disorders
  - Depression
  - Obsessive-compulsive disorder
  - Psychomotor disorders
  - Schizophrenia
- Pyogenic infections, including:
  - Aspergillosis
  - Encephalitis
- Substance abuse, including the CNS effects of alcohol, cocaine, and heroin
- Trauma, including brain injury and carbon monoxide poisoning

- Viral infections, including:
  - HIV/AIDS
  - AIDS dementia complex
  - Creutzfeldt-Jakob syndrome
  - Progressive multifocal leukoencephalopathy
  - Progressive rubella encephalopathy
  - Subacute sclerosing panencephalitis
- Mycobacterium infection
- Migraine
- Anorexia nervosa
- Assessment of cerebral blood flow in newborns
  - Vegetative versus "locked-in" state

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

Musculoskeletal diseases
- Spondylodiscitis
- Joint replacement follow-up

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

Policy Guidelines

In individuals with epileptic seizures, appropriate candidates are individuals with complex partial seizures who have failed to respond to medical therapy and have been advised to have a resection of a suspected epileptogenic focus located in a region of the brain accessible to surgery. Further, for the purposes of this review, conventional noninvasive techniques for seizure localization must have been tried with results suggesting a seizure focus but not sufficiently conclusive to permit surgery. The purpose of the positron emission tomography (PET) examination should be to avoid subjecting the individual to extended preoperative electroencephalographic recording with implanted electrodes or to help localize and minimize the number of sites for implanted electrodes to reduce the morbidity of that procedure.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

78608	78609	78811	78812	78813	78814
78815	78816	A9552			

Other codes (investigational, not medically necessary, etc.):

A9601	A9602	Q9982	Q9983

Rationale

This review was informed in part by 3 TEC Assessments (1996) that addressed various applications of positron emission tomography (PET).(5-7)

Intractable Epilepsy

Clinical Context and Test Purpose
The purpose of fluorine 18 fluorodeoxyglucose PET (FDG-PET) in patients with epilepsy is to inform the decision on selecting treatment regimens.

The question addressed in this evidence review is: Does the use of FDG-PET improve the net health outcome in individuals with medically refractory or intractable epilepsy who are candidates for neurosurgery?

The following PICO was used to select literature to inform this review.

Populations
The population of interest includes patients with intractable epilepsy.

Approximately one-third of patients with epilepsy do not achieve adequate seizure control with antiepileptic drugs.(8) Individuals with drug-resistant epilepsy are candidates for other treatments such as surgery. Many effective surgical procedures are available, and the treatment selected depends on characteristics of the seizures (e.g., 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 (CT), electric and magnetic source imaging, and magnetic resonance spectroscopy, 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 the distribution of glucose uptake in the brain, presumably detecting focal areas of decreased metabolism.(9) PET may be able to correctly identify the focus in patients with unclear or unremarkable MRI results or discordant MRI and electroencephalographic results that could reduce the need for invasive electroencephalography. PET scanning may also help to predict which patients will have a favorable outcome following surgery. The Engel classification system often used to describe the surgical outcome, is as follows: class I: seizure-free (or free of disabling seizures); class II: nearly seizure-free; class III: worthwhile improvement; and class IV: no worthwhile improvement.(10)

Interventions
The intervention of interest is FDG-PET. For patients with epilepsy, FDG-PET would be conducted prior to surgery to identify the epileptogenic focus.

Comparators
Ictal scalp electroencephalography and MRI are currently being used to make preoperative decisions in patients with epilepsy for whom surgery is being considered.

Outcomes
For patients with epilepsy, the outcome of interest is to predict which patients will have a favorable outcome following surgery. Other outcomes of interest include symptoms, change in disease status, functional outcomes, health status measures, quality of life (QOL), hospitalizations, medication use, and resource utilization. For patients with epilepsy, FDG-PET would be conducted prior to surgery.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

Clinical Validity
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systemic Reviews
A TEC Assessment (1996) reviewed the 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.(7) 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%. Reviewers 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. Tables 1 and 2 summarize the characteristics and results of several meta-analyses of FDG-PET published since that TEC Assessment that have assessed either presurgical planning of patients who are candidates for epilepsy surgery or prediction of surgical outcomes. A brief discussion of each trial follows.

Table 1. Characteristics of Systematic Reviews Assessing Use of FGD-PET for Epilepsy

Study	Dates	Trials	N (Range)	Design	Duration
Niu et al (2021)	1995-2020	44	2246 (6-194)	NR	NR
Jones et al (2016)	1946-2014	27	3163 (25-434)	OBS	≥ 1 year
Wang et al (2016)	2000-2015	18	391 (5-86)	NR	1-6.5 years
Burneo et al (2015)	1946-2013	39	2650	OBS	1 year, median
Englot et al (2012)	1990-2010	21[a]	1199 (13-253)[a]	OBS	> 4 years
Willmann et al (2007)	1992-2006	46	1112 (2-117)	OBS	3 to 144 months

FDG-PET: fluorine 18 fluorodeoxyglucose positron emission tomography; OBS: observational; NR: not reported.
[a] Total number of studies and participants included; unclear if all studies included PET as a predictor.

Niu et al (2021) conducted a meta-analysis of studies that described the concordance of FDG-PET with other methods (EEG and surgery) of identifying the epileptogenic zone in patients with epilepsy(11) A total of 44 studies (N=2246) of FDG-PET, FDG-PET/MRI, or ^{11}C-flumazenil-PET were identified. All but 3 studies used FDG-PET and the majority used ^{18}FFDG-PET. Results are summarized in Table 2. Pooled sensitivity and specificity of FDG-PET were 0.66 (95% confidence interval [CI], 0.58 to 0.73) and 0.71 (95% CI, 0.63 to 0.78), respectively.

Jones et al (2016) published a systematic review of neuroimaging for surgical treatment of temporal lobe epilepsy.(12) 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. Reviewers searched EMBASE, PUBMED, 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.

Wang et al (2016) conducted a systematic review of prognostic factors for seizure outcomes in patients with MRI-negative temporal lobe epilepsy that included a search of PubMed.(13) Eighteen studies (N=391 patients) were included with a mean or median follow-up of more than 1 year. 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 the summary results.

Burneo et al (2015) published a recommendation report for the Program in Evidence-based Care 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.(14) The literature review included searches of the PubMed, EMBASE, and OVID, and Cochrane databases. Systematic reviews, RCTs, and observational studies that evaluated the use of FDG-PET in medically intractable epilepsy were eligible for inclusion. Reviewers included 39 observational studies (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.

Englot et al (2012) performed a systemic review of predictors of long-term seizure freedom after surgery for frontal lobe epilepsy; they included articles found through a PUBMED search that had at least 10 participants and 48 months of follow-up.(15) Long-term seizure freedom was defined as Engel class I outcome. Twenty-one studies (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 scans did not predict seizure freedom.

Willmann et al (2007) conducted a meta-analysis on the use of FDG-PET for preoperative evaluation of adults with temporal lobe epilepsy, which included 46 studies identified through a PubMed search.(16) 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. Reviewers 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.

Table 2. Results of Systematic Reviews on Use of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography for Epilepsy

Study	Studies	N	Outcomes	Estimate or Range	95% CI	I^2	p
Niu et al (2021)	44	2246	Concordance with reference standard (EEG or surgical outcome)	Pooled concordance (overall), 0.67	0.60 to 0.73	90.5%	0.00
Jones et al (2016)	11	1358	Surgical outcome	• No overall summary given • Reported conflicting findings on prognostic importance of PET-identified focal hypometabolism	No pooling		
Wang et al (2016)	5	NR	Surgical outcome (freedom from seizures)	OR for PET hypometabolism positive vs negative, 2.11	0.95 to 4.65	0	0.06
Burneo et al (2015)	8	310	Percent agreement, localization with PET vs EEG	• 56%-90% overall (adults) • 63%-90% in temporal lobe epilepsy (adults)	No pooling		
	13	1064	Prognostic accuracy (good surgical outcome)	36%-89% (adults)	No pooling		
	6	690	Clinical decisions (influence decision making)	• 53%-71% (adults) • 51%-95% (children)	No pooling		
Englot et al (2012)	21[a]	1199[a]	Prognostic accuracy (good surgical outcome)	% for PET focal vs PET nonfocal, 52% vs 48%	NR	NR	0.61
Willmann et al (2007)	46	1112	Prognostic accuracy (good surgical outcome)	PPV=86%	NR	NR	NR

CI: confidence interval; EEG: electroencephalography; NR: not reported; OR: odds ratio; PET: positron emission tomography; PPV: positive predictive value.
[a] Total number of studies and participants included; unclear if all studies included PET as a predictor.

Observational Studies
Traub-Weidinger et al (2016) reviewed a database of pediatric patients with epilepsy who underwent hemispherotomy and were evaluated with both FDG-PET and MRI before surgery (n=35).(17) Identifying the hemisphere harboring the epileptogenic zone before surgery has been shown to improve surgical outcomes. Seizure outcomes were measured using International League Against Epilepsy classifications. At 12 months post-surgery, 100% of patients with unilateral FDG-PET hypometabolism were seizure-free, while 95% of patients with unilateral lesions identified by MRI were seizure-free. For patients with bilateral FDG-PET hypometabolism, 75% were seizure-free at 12 months, while 71% of patients with bilateral lesions identified by MRI were seizure-free.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

The recommendation report by Burneo et al (2015) discussed 3 retrospective studies demonstrating the impact of FDG-PET on clinical management of adults with epilepsy and three retrospective studies on change in clinical management based on FDG-PET results in children with epilepsy.(14) After receiving FDG-PET results on adults, some clinicians changed surgical decisions, used the results to guide intracranial EEGs, and ruled out an additional evaluation of the patient. Among pediatric patients who underwent FDG-PET, clinicians reported using the results to alter surgical decisions, classify symptomatic infantile spasms, and avoid invasive monitoring due to localizing information. The study results were not pooled due to heterogeneity among the study designs and patient populations.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Intractable Epilepsy
The TEC Assessment and Program in Evidence-Based Care 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. There were several retrospective studies that surveyed clinicians on the utility of FDG-PET in managing patients with epilepsy. In general, the clinicians reported that the information from FDG-PET was helpful in surgical management decisions. Only observational studies are available, most having small samples sizes with varying patient characteristics and definitions of good surgical outcomes.

Suspected Chronic Osteomyelitis

Clinical Context and Test Purpose

The purpose of FDG-PET in patients with chronic osteomyelitis is to confirm a diagnosis or to inform the decision on selecting treatment regimens.

The question addressed in this evidence review is: Does the use of FDG-PET improve the net health outcome in individuals with chronic osteomyelitis?

The following PICOs were used to select literature to inform this review.

Populations

The population of interest are patients with 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 an 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 a probe-to-bone test, which involves exploring the wound for palpable bone using a sterile blunt metal probe.(18) 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. Neither MRI nor computed tomography (CT), both of which have high sensitivity in diagnosing osteomyelitis, can be used in patients with metal hardware.(19) 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 arthropathy.

Interventions

The intervention of interest is FDG-PET. For patients with suspected chronic osteomyelitis, FDG-PET would be performed following inconclusive clinical examinations and standard radiographs.

Comparators

CT, radiography, and MRI are currently being used to make decisions about managing suspected chronic osteomyelitis.

Outcomes

For patients with suspected chronic osteomyelitis, the main outcomes interest are disease-related morbidity and mortality. Other outcomes of interest include test accuracy, test validity, symptoms, change in disease status, functional outcomes, health status measures, QOL, hospitalizations, medication use, and resource utilization.

Study Selection Criteria

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described

- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systemic Reviews
Llewellyn et al (2020) conducted a systematic review and meta-analysis of 36 studies that reported the accuracy of imaging modalities for diagnosing osteomyelitis in patients with diabetic foot ulcer.(20) Various imaging techniques were included: PET, MRI, CT, x-rays, planar scintigraphy, ultrasound, and single-positron emission computed tomography. Analysis of the 6 studies that used PET showed high specificity (92.8%; 95% CI, 75.7 to 98.2; I^2 = 0%) and moderate sensitivity (84.3%, 95% CI, 52.8 to 96.3; I^2 = 0%). The overall positive rate for PET was 45.9% (95% CI, 27.81 to 75.69; I^2 = 36%, which was lower than other modalities including MRI and scintigraphy. PET had a PPV of 88.6% and negative predictive value (NPV) of 85.4%. The authors concluded that PET had similar diagnostic accuracy to MRI for diagnosing osteomyelitis.

Lauri et al (2017) published a systematic review of 27 trials of diabetic patients with suspicion of osteomyelitis of the foot that compared the diagnostic performance of several imaging techniques.(21) MRI, technetium 99m hexamethylpropyleneamineoxime white blood cell (WBC) scan, indium In 111 oxyquinoline WBC scan, or FDG-PET plus CT were assessed. In this population, the sensitivity and specificity of FDG-PET/CT (6 studies; 254 patients) were 89% (95% CI, 68% to 97%) and 92% (95% CI, 85% to 96%), respectively. The diagnostic odds ratio for FDG-PET was 95, and the positive and negative likelihood ratios were 11 and 0.11, respectively. Of the 4 modalities included, FDG-PET/CT and technetium 99m hexamethylpropyleneamineoxime WBC scans had greater specificity (both 92%) than MRI or indium In 111 oxyquinoline WBC scans (both 75%). Sensitivity did not differ significantly between modalities: 93% for MRI, 92% for indium In 111 oxyquinoline WBC, 91% for technetium 99m hexamethylpropyleneamineoxime WBC, and 89% for FDG-PET. The review was limited by the small size of studies included, which precluded subgroup or meta-regression analyses.

A systematic review by Treglis et al (2013) assessed 9 studies (n=299 patients), FDG-PET and PET with CT were found to be useful for assessing suspected osteomyelitis in the foot of patients with diabetes.(22) A meta-analysis of four 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 summary area under the receiver operating characteristic curve (AUROC) was 0.874.

Termaat et al (2005) conducted a systematic review and of diagnostic imaging to assess chronic osteomyelitis.(21) Reviewers assessed 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, (N=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" (24); (2) 22 trauma patients scheduled for surgery who had suspected metallic implant-associated infection (23); (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 (24); and (4) 30 consecutive nondiabetic patients referred for possible chronic osteomyelitis.(27) The results appeared to be robust across fairly diverse clinical populations, which strengthen the conclusions.

Prospective Studies

Rastogi et al (2016) published a study comparing the efficacy of FDG-PET plus CT with contrast-enhanced MRI in the detection of diabetic foot osteomyelitis in patients with Charcot neuroarthropathy.(28) Patients with suspected diabetic foot osteomyelitis (N=23) underwent radiographs, FDG-PET/CT, and contrast-enhanced MRI. Bone culture, which is considered the criterion standard, identified 12 of the 23 patients with osteomyelitis. The sensitivity, specificity, PPV, and NPV of FDG-PET/CT in diagnosing osteomyelitis were 83%, 100%, 100%, and 85%, respectively. The same measures for contrast-enhanced MRI were 83%, 64%, 71%, and 78%, respectively.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs identified assessed the evidence on the clinical utility of FDG-PET for diagnosing osteomyelitis.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Diagnosing osteomyelitis is challenging and FDG-PET may provide additional information along the diagnostic pathway. Currently, bone biopsy is considered the reference standard, and radiographs are often used as screening tests prior to bone biopsy. When radiographs are inconclusive, other imaging techniques have been used, such as MRI and CT. While MRI has been shown to have a high sensitivity in diagnosing osteomyelitis, FDG-PET has also been shown to have high sensitivity and can be used when MRI is inconclusive or not possible (e.g., patients with metal hardware).

Section Summary: Suspected Chronic Osteomyelitis

Evidence for the use of FDG-PET to diagnose chronic osteomyelitis includes 4 systematic reviews and a prospective study published after the systematic reviews. FDG-PET and FDG-PET/CT were found to have high specificity and PPVs in diagnosing osteomyelitis. Compared with other modalities, FDG-PET and FDG-PET/CT were found to have better diagnostic capabilities than contrast-enhanced MRI.

Diagnosing Suspected Alzheimer's Disease

Clinical Context and Test Purpose

The purpose of FDG-PET in patients with suspected AD is to confirm a diagnosis of AD. The question addressed in this evidence review is: Does the use of FDG-PET improve the net health outcome in individuals with suspected AD?

The following PICO was used to select literature to inform this review.

Populations

The population of interest are patients with suspected AD.

A definitive diagnosis of AD requires histopathologic examination of brain tissue obtained by biopsy or autopsy. In practice, clinical criteria based on clinical examination, neurologic 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 distinguish AD from other forms of dementia.

Interventions

The intervention of interest is FDG-PET.

For patients with suspected AD, FDG-PET would be performed following inconclusive clinical examinations and standard radiographs.

Comparators

Clinical diagnosis without FDG-PET is currently being used for suspected AD.

Outcomes

For patients with suspected AD, the main outcomes interest are test validity, symptoms, change in disease status, functional outcomes, health status measures, and quality of life.

Study Selection Criteria

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

This evidence review does not discuss PET tracers that bind to amyloid beta plaques.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Summaries of characteristics and results of several meta-analyses of early diagnosis of Alzheimer disease (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. Characteristics of Systematic Reviews on Use Assessing FDG-PET for AD and Dementia

Study	Dates	Studies	N (Range)	Design	Outcomes
Zhu et al (2022)	Up to 2020	16	NR	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Smailagic et al (2015)	1999-2013	16	697 (19-94)	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Davison et al (2014)	Up to 2013	8	197 (7-199)	OBS	Diagnostic accuracy for diagnosis of AD, differential diagnosis in dementia, predicting conversion from MCI to AD
Bloudek et al (2011)	1990-2010	119	NR	OBS	Diagnostic accuracy for diagnosis of AD, differential diagnosis in dementia
Yuan et al (2009)	2001-2005	6	280 (17-128)	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Matchar et al (2001)	1995-2001	18	1018 (10-138)	OBS	Diagnostic accuracy for distinguishing AD from healthy controls and for differential diagnosis in dementia

AD: Alzheimer disease; FDG-PET: fluorine 18 fluorodeoxyglucose positron emission tomography; MCI: mild cognitive impairment; NR: not reported; OBS: observational.

Zhu et al (2022) conducted a meta-analysis of cerebral perfusion imaging methods (FDG-PET, SPECT, and MRI) in the assessment of MCI conversion to AD. A total of 16 studies were included (5 with FDG-PET).(86) The authors found significantly higher sensitivity, specificity, and positive likelihood ratio with FDG-PET than SPECT or MRI. The studies for FDG-PET were determined to have low risk of bias.

Sailagic et al (2015) conducted a Cochrane review to assess the diagnostic accuracy of FDG PET for detecting people who clinically convert to Alzheimer disease dementia or other forms of dementia at follow-up.(81) 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 positive findings based on PET scans and studies used mixed thresholds for diagnosis, reviewers used a hierarchical summary receiver operating characteristic curve to derive 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 ranged between 46% and 95% while the specificities were between 29% and 100%; however, a meta-analysis could not be conducted because of the small number of studies sample sizes. Reviewers indicated that most studies were poorly reported and had an unclear risk of bias, mainly for the reference standard and participant selection domains.

In a systematic review (quality assessment of included studies was not reported), Davison et al (2014) reported on studies on the diagnostic performance of FDG-PET and single-photon emission computed tomography (SPECT) identified through a PUBMED search.(82) Three studies (197 patients) used histopathology as the 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 three 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 two 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) assessed diagnostic strategies for AD in a meta-analysis.(83) Reviewers included 119 studies of diagnostic performance characteristics published from 1990 to 2010. Studies were identified through a search of PUBMED 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.

In a meta-analysis, Yuan et al (2009) compared the prognostic capacity of FDG-PET, SPECT, and structural MRI to predict patients' conversion from MCI to AD.(84) Using 24 articles (total n=1112 patients) published between 1990 to 2008 (6 studies with 280 patients on FDG-PET, published 2001-2005), reviewers 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 (e.g., publication year, age, male-female ratio, follow-up interval, years of education, mean Mini-Mental State Examination score at baseline) yielded no significant results.

Using decision-analysis modeling, Matchar et al (2001) performed a technology assessment for the Agency for Healthcare Research and Quality to examine whether the use of FDG-PET would improve health outcomes for diagnosis of AD in three clinical populations: patients with dementia, patients with MCI, and subjects with no symptoms but with a first-degree relative with AD.(85) For the review, a search was performed using PUBMED, CINAHL, and the HealthSTAR databases. Eighteen articles (total n=1018 participants) were included. The reference standard used in the studies was either histopathology or clinical diagnosis. Studies reported on various cutoffs for PET positivity, and therefore, an unweighted summary receiver operating characteristic method was used to calculate the pooled area under the curve. Results are summarized in Table 4. Reviewers concluded that outcomes for all 3 groups were better if all patients were treated with agents such as cholinesterase inhibitors rather than limiting treatment to patients based on FDG-PET results. The rationale was that the complications of treatment were relatively mild, and treatment was considered to have some degree of efficacy in delaying the progression of AD.

Table 4. Results of Systematic Review on Use Assessing FDG-PET for AD and Dementia

Study	Studies	N	Outcomes	Estimate (95% CI)
Zhu et al (2022)	5a	NR	Diagnostic accuracy	• Sensitivity: 87.2% (81.3% to 92.1%) • Specificity: 89.35% (77.6% to 91.8%) • PLR: 5.973 (3.15 to 6.72) • NLR: 0.132 (0.05 to 0.49)
Smailagic et al (2015)	14	421	Diagnostic accuracy	• Sensitivity range: 25%-100% • Specificity range: 15%-100% • PLR: 4.03 (2.97 to 5.47) • NLR: 0.34 (0.15 to 0.75)
Davison et al (2014)	3	197	Diagnostic accuracy	• Sensitivity: 84% • Specificity: 74%
	2	183	Diagnostic accuracy, predicting conversion from MCI to AD	• Sensitivity range: 57%-82% • Specificity range: 67%-78%
	5	292	Diagnostic accuracy, differentiating AD and LBD	• Sensitivity range: 83%-92% • Specificity range: 67%-93%
Bloudek et al (2011)	20	NR	Diagnostic accuracy	• Sensitivity: 90% (84% to 94%) • Specificity: 89% (81% to 94%)
	13	NR	Diagnostic accuracy, AD vs other dementia	• Sensitivity: 92% (84% to 96%) • Specificity: 78% (69% to 85%)
Yuan et al (2009)	6	280	Diagnostic accuracy	• Sensitivity: 89% (92% to 94%) • Specificity: 85% (78% to 90%) • PLR: 4.6 (3.2 to 6.7) • NLR: 0.15 (0.05 to 0.48)
Matchar et al (2001)	15	729	Diagnostic accuracy	• Sensitivity: 88% (79% to 94%) • Specificity: 87% (77% to 93%)
	3	289	Diagnostic accuracy, distinguishing AD from non-AD dementia	• Sensitivity range: 86% to 95% • Specificity range: 61% to 74%

AD: Alzheimer disease; CI: confidence interval; FDG-PET: fluorine 18 fluorodeoxyglucose positron emission tomography; LBD: Lewy body dementia; MCI: mild cognitive impairment; NLR: negative likelihood ratio; NR; not reported; PLR: positive likelihood ratio.
a Includes only the 5 studies with FDG-PET.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Review of Evidence

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Motara et al (2017) assessed the accuracy of dual-trained radiologists and nuclear medicine physicians to diagnose the type of cognitive impairment based on FDG-PET/CT images.

Records of patients who had undergone FDG-PET/CT because of cognitive impairment (AD, frontotemporal dementia, mixed dementia, and dementia with Lewy bodies) following a negative CT or MRI were reviewed (n=136).(87) Questionnaires were sent to the referring physicians to gather information on the final clinical diagnosis, usefulness of the PET/CT report, and whether the report impacted clinical management. Response rate was 72% (98/136) and mean patient follow-up was 471 days. For the diagnosis of AD, using the final clinical diagnosis as the reference standard, the sensitivity, specificity, PPV, and NPV were 87%, 97%, 93%, and 91%, respectively. Questionnaires received from the 98 physicians indicated that PET/CT: was useful (78%); had an impact on clinical management (81%); added confidence to the pretest clinical diagnosis (43%); reduced the need for further investigations (42%); changed the pretest clinical diagnosis (35%); and led to a change in therapy (32%).

The American College of Radiology indicates that advanced imaging modalities (i.e., FDG-PET) are not routinely used in community or general practices for the diagnosis or differentiation of forms of dementia.(92) However, FDG-PET may be useful in select circumstances as a problem-solving technique to direct management. The European Federation of Neurological Societies recommends its use in those cases where the diagnosis remains in doubt after clinical and structural MRI workup and in particular clinical settings.(94) Gauthier et al (2012) discussed the recommendations made by the National Institute on Aging – Alzheimer Association workgroups at the 4th Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia. An 18F-FDG PET was determined to be useful in forming a differential diagnosis for a patient with a diagnosis of dementia who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a dementia specialist but whose underlying pathological process is still unclear, preventing adequate clinical management (Grade 1B).(95)

Section Summary: Suspected Alzheimer Disease

Several systematic reviews offer 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. A single study was identified that surveyed physicians on the clinical utility of FDG-PET/CT in managing patients with cognitive impairment. In general, the physicians found the FDG-PET/CT helpful, but no clinical outcomes of patients were reported.

Suspected Large Vessel Vasculitis

Clinical Context and Test Purpose

The purpose of FDG-PET in patients with suspected large vessel vasculitis (LVV) is to confirm a diagnosis or to inform the decision on selecting treatment regimens.

The question addressed in this evidence review is: Does the use of FDG-PET improve the net health outcome in individuals with suspected LVV?

The following PICO was used to select literature to inform this review.

Populations
The populations of interest include patients with suspected LVV.

LVV causes granulomatous inflammation primarily of the aorta and its major branches.(29) There are two major types of LVV: giant cell arteritis (GCA) and Takayasu arteritis (TA). Classification criteria for GCA and TA were developed by American College of Rheumatology (ACR) in 1990.(30,31) The definitions have since been refined by the International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides (2012).(32) Biopsy and angiography are considered the criterion standard techniques for diagnosis, but they are invasive and detect changes that occur late in the 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.(33) Misdiagnosis is common particularly during the early stages of the disease. Unfortunately, late diagnosis can lead to serious aortic complications and death. Since activated 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.

Interventions
The intervention of interest is FDG-PET. For patients with suspected LVV, FDG-PET would be performed following inconclusive clinical examinations and standard radiographs.

Comparators
Clinical diagnosis without FDG-PET is currently being used to make decisions about suspected LVV.

Outcomes
For patients with suspected LVV, the main outcomes of interest are disease-related morbidity and mortality. Other outcomes of interest include test accuracy, test validity, symptoms, change in disease status, functional outcomes, health status measures, QOL, hospitalizations, medication use, and resource utilization.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
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. Characteristics of Systematic Reviews on Use of FDG-PET for Large Vessel Vasculitis

Study	Dates	Studies	N (Range)	Design	Outcomes

Van der Geest et al (2021)	1987-2020	21	798 (11-112)	OBS	Diagnostic accuracy for relapsing/refractory disease
Lee et al (2016)	Up to 2015	8	400 (21-93)	OBS	Diagnostic accuracy for GCA and TA
Soussan et al (2015)	2000-2013	21	712 (18-93)	OBS	Diagnostic accuracy for GCA; assessment of disease activity in TA
Puppo et al (2014)	1999-2014	19	977 (8-304)	OBS	Diagnostic accuracy for GCA
Treglia et al (2011)	Up to 2011	32	604	OBS	Diagnostic accuracy for GCA and TA; assessment of disease activity; monitor treatment response
Besson et al (2011)	Up to 2011	14	Unclear	OBS	Diagnostic accuracy for GCA

FDG-PET: fluorine 18 fluorodeoxyglucose positron emission tomography; GCA: giant cell arteritis; OBS: observational; TA: Takayasu arteritis.

A meta-analysis by van der Geest et al (2021) evaluated the diagnostic accuracy of FDG-PET/CT for monitoring LVV treatment response.(34)The investigators identified 21 studies for systematic review and 8 studies for meta-analysis. Most studies used ACR criteria as the reference standard. An analysis of 4 studies (N=111 patients with 136 scans) showed that FDG-PET/CT had a sensitivity and specificity of 77% and 71%, respectively for distinguishing between active disease and clinical remission. A summary of the results is presented in Table 4.

Lee et al (2016) performed a meta-analysis of the diagnostic accuracy of FDG PET or PET/CT for LVV.(35) The search included studies indexed in PubMed, EMBASE, or Cochrane Library that used the ACR classification system as the reference standard diagnosis. Eight studies were (N=400 participants) were identified for inclusion. 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.

Soussan et al (2015) conducted a literature review assessing the role of FDG-PET in the management of LVV, focused on three issues: determining the FDG-PET criteria for diagnosing 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.(36) The PUBMED, Cochrane Library, and EMBASE databases were searched for articles that evaluated the value of FDG-PET in LVV. Selection criteria included the use of the ACR classification for GCA or TA, the definition of a positive amyloid threshold for PET, and more than four 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 (40) 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 systematic review by Puppo et al (2014) included studies of FDG-PET in GCA comparing the diagnostic performance of qualitative and semiquantitative methods of FDG-PET interpretation.(37) Reviewers selected 19 studies (442 cases, 535 controls) found in PubMed or the Cochrane Library. The selected studies had various reference standards. Ten used qualitative FDG uptake criteria to characterize inflammation, six used semiquantitative criteria, and three 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.

Treglia et al (2011) published a systematic review of PET and PET/CT in patients with LVV.(38) Reviewers searched PUBMED and Scopus for publications on the role of FDG-PET in LVV. Reviewers identified 32 studies (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. 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; and (3) the role of these imaging methods in monitoring treatment response is unclear. Reviewers 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 for patients with suspected GCA based on a search of PUBMED, EMBASE, and the Cochrane databases.(39) Studies were included if they evaluated the performance of FDG-PET for the diagnosis of GCA, had at least eight 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. Results of Systematic Reviews Assessing Use of FDG-PET for LVV

Study	Studies	N	Outcomes	Estimate (95% CI)
van der Geest et al (2021)	21	798	Diagnostic accuracy of FDG-PET/CT for relapsing/refractory disease	• Sensitivity: 77% (57%-90%) • Specificity: 71% (47%-87%) • PLR: 2.65 (1.16-6.08) • NLR: 0.32 (0.13-0.80)
Lee et al (2016)	8	400	Diagnostic accuracy of PET and PET/CT for GCA and TA	• Sensitivity: 76% (68% to 82%) • Specificity: 93% (89% to 96%) • PLR: 7.27 (3.71 to 14.24) • NLR: 0.30 (0.23 to 0.40)
	3	133	Diagnostic accuracy of PET and PET/CT for GCA	• Sensitivity: 83% (72% to 91%) • Specificity: 90% (80% to 96%) • PLR: 7.11 (2.91 to 17.4)

				• NLR: 0.20 (0.11 to 0.34)
Soussan et al (2015)	4	233	Diagnostic accuracy for GCA	• Sensitivity: 89.5% (78.5% to 96.0%) • Specificity: 97.7% (94% to 99%) • PLR: 28.7 (11.5 to 71.6) • NLR: 0.15 (0.07 to 0.29)
	7	237	Diagnostic accuracy for disease activity in TA	• Sensitivity: 87% (78% to 93%) • Specificity: 73% (63% to 81%) • PLR: 4.2 (1.5 to 12) • NLR: 0.2 (0.1 to 0.5)
Puppo et al (2014)	10	633	Diagnostic accuracy for GCA	• Sensitivity range: 56%-77% • Specificity range: 77%-100% • PPV range: 93%-100% • NPV range: 70%-82%
	6	282	Diagnostic accuracy for GCA	• Sensitivity range: 58%-90% • Specificity range: 42%-95% • PPV range: 79%-89% • NPV range: 95%-98%
	3	72	Diagnostic accuracy for GCA	• Sensitivity range: 65%-100% • Specificity range: 45%-100%
Treglia et al (2011)[42]	32	604	Diagnostic accuracy for GCA and TA; assessment of disease activity; monitor treatment response	• No pooling; concluded that FDG-PET is useful "in the initial diagnosis and in the assessment of activity and extent of disease in patients with LVV"
Besson et al (2011)[43]	6	283	Diagnostic accuracy for GCA	• 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)

CI: confidence interval; CT: computed tomography; FDG: fluorine 18 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.

Observational Studies

Sammel et al (2019) evaluated the accuracy of FDG-PET/CT as a first-line test for GCA in the 'Giant Cell Arteritis and PET Scan' (GAPS) study.(41) The GAPS study prospectively enrolled 64 patients with newly suspected GCA from 13 sites in Sydney, Australia between May 2016 and July 2018. Blinded physicians rated the FDG-PET scans as globally positive or negative for GCA and their ratings were compared to temporal artery biopsy and clinical diagnosis at 6 months. Sensitivity was 92% (95% CI, 62% to 100%) compared with temporal artery biopsy and 71% (95% CI, 48% to 89%) compared to clinical diagnosis. Specificity was 85% (95% CI, 71% to 94%) compared to temporal artery biopsy and 91% (95% CI, 78% to 97%)- compared to clinical diagnosis. Interpretation of these findings is limited by the small sample size, as evidenced by the wide 95% confidence intervals.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs identified assessed the evidence on the clinical utility of FDG-PET for diagnosing LVV.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of FDG-PET for diagnosing LVV has not been established, a chain of evidence supporting its clinical utility cannot be constructed.

Section Summary: Suspected Large Vessel Vasculitis

Several systematic reviews and an observational study have evaluated the diagnosis and management of GCA using FDG-PET. Most studies selected were small, many lacked controls and results were heterogeneous. Studies comparing PET with the true reference standard (biopsy or angiography) are 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

Clinical Context and Test Purpose

The purpose of FDG-PET in patients with diverse noncardiac or nononcologic conditions is to confirm a diagnosis or to inform the decision on selecting treatment regimens.

The question addressed in this evidence review is: Does the use of FDG-PET improve the net health outcome in individuals with diverse noncardiac or nononcologic conditions?

The following PICO was used to select literature to inform this review.

Populations

The populations of interest include patients with diverse noncardiac or nononcologic conditions (e.g., central nervous system, pulmonary, and musculoskeletal diseases).

Interventions

The intervention of interest is FDG-PET.
For patients with diverse noncardiac or nononcologic conditions, FDG-PET would be performed following inconclusive clinical examinations and standard radiographs.

Comparators

CT, radiograph, and MRI are currently being used to make decisions about managing diverse noncardiac or nononcologic conditions.

Outcomes

For patients with diverse noncardiac or nononcologic conditions, the main outcomes of interest are disease-related morbidity and mortality. Other outcomes of interest include test accuracy, test validity, symptoms, change in disease status, functional outcomes, health status measures, QOL, hospitalizations, medication use, and resource utilization.

Study Selection Criteria

Methodologically credible studies were selected using the principles described in the first indication.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews
Numerous systematic reviews have described the use of PET in patients with carotid stenosis;(42) inflammatory diseases;(43-47) fever of unknown origin;(48-50) hyper insulinemic hypoglycemia;(51,52) spondylodiscitis;(53) spinal infections;(54) mycobacterium infection;(55) Creutzfeldt-Jakob disease;(56) vascular prosthetic graft infection;(57-59) prosthetic infection after knee or hip arthroplasty;(60,61) inflammatory bowel disease;(62) atypical parkinsonism;(63) and, Huntington disease.(64) Many studies cited in these reviews were small, retrospective, and lacked standard definitions of PET interpretation and positivity; many did not directly compare one modality with another in the same patient group or correlate the PET results in individual patients to improved clinical outcomes.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs identified assessed the evidence on the clinical utility of FDG-PET for diagnosing diverse noncardiac or nononcologic conditions.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of FDG-PET for diagnosing diverse noncardiac or nononcologic condition has not been established, a chain of evidence supporting its clinical utility cannot be constructed.

Section Summary: Diverse Noncardiac and Nononcologic Conditions
Systematic reviews have assessed the use of FDG-PET or FDG-PET/CT for diagnosing or managing carotid stenosis, various inflammatory and immune-mediated diseases, fever of unknown origin, and various infections. However, studies included in these reviews are mostly small, retrospective, and lack standard definitions of PET interpretation and positive findings. Few studies compared PET with other diagnostic modalities and no studies have reported on patient clinical outcomes. The exception being support for differentiating FTD from Alzheimer's

in patients with a diagnosis of dementia who have undergone the recommended baseline clinical and structural brain imaging evaluation and who have been evaluated by a dementia specialist but whose underlying pathological process is still unclear.

SUMMARY OF EVIDENCE

For individuals with epileptic seizures who are candidates for surgery who undergo FDG-PET, the evidence includes systematic reviews (following 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 positron emission tomography (PET) recommendation report all concluded that FDG-PET accurately localizes the seizure focus compared with 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 that the technology results in an improvement in the net health outcome.

For individuals with suspected chronic osteomyelitis who receive FDG-PET, the evidence includes meta-analyses and a prospective study published after the meta-analyses. The 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 from 2013 of nine studies revealed that 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 that FDG-PET was the most accurate mode (pooled sensitivity, 96%; pooled specificity, 91%) 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 that the technology results in an improvement in the net health outcome.

For individuals who have suspected Alzheimer disease (AD) who receive FDG-PET to diagnose AD, the evidence includes systematic reviews of nonrandomized studies. Relevant out comes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, and quality of life. The studies included in the reviews were generally of poor quality. There is no standard cutoff for FDG-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 using FDG-PET with the clinical diagnosis not using FDG-PET. Therefore, the incremental value of adding FDG-PET to the standard clinical diagnosis is unclear. No studies have reported on clinical outcomes of patients diagnosed with and without FDG-PET. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have been diagnosed with dementia but whose underlying pathological process is still unclear after a baseline imaging and evaluation by a dementia specialist, FDG-PET was given a Grade 1B recommendation by the National Institute on Aging for the differentiation of frontotemporal dementia from Alzheimer's disease. The technology may result in an improvement in the net health outcome of a specified group.

For individuals with suspected large vessel vasculitis who receive FDG-PET, the evidence includes 6 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 an improvement in the net health outcome.

For individuals with diverse noncardiac or nononcologic conditions (e.g., 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; further, many studies did not directly compare a modality with another in the same patient group - nor did they correlate PET results in individual patients with improved clinical outcomes. Additional studies are needed to demonstrate that FDG-PET results can change management, and therefore improve patient outcomes to support the utility of FDG-PET. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Neurology

Evidence-based practice parameters from the American Academy of Neurology (AAN) are summarized in Table 7.

Table 7. Practice Parameters on Diagnosis of Dementia

Practice Parameter	Date	PET Recommendation
Diagnosis of dementia[92]	2004: reaffirmed	PET imaging not recommended for routine use in diagnostic evaluation of dementia (LOR: moderate clinical certainty)
Early detection of dementia[92]	2003: reaffirmed	Not addressed
Diagnosis of new-onset PD[92,93]	2006: reaffirmed 2013; retired 2016	Evidence insufficient to support or refute FDG-PET as a means of distinguishing PD from other parkinsonian syndromes
Evaluation of depression, psychosis, and dementia in PD[90,]	2006; retired 2018	Not addressed
Mild cognitive impairment[89,91]	2001; 2017; 2018	Not addressed

FDG: fluorine 18 fluorodeoxyglucose; LOR: level of recommendation; PD: Parkinson disease; PET: positron emission tomography.

American Academy of Orthopaedic Surgeons

The American Academy of Orthopaedic Surgeons (AAOS) (2019) published evidence-based, consensus guidelines on the diagnosis and prevention of periprosthetic joint infections.(65) The AAOS recommendation regarding FDG- PET is that there is limited strength of evidence supporting the use of FDG PET/CT to aid in the diagnosis of periprosthetic joint infections. The strength of the recommendation was rated as "limited," which was described as "Evidence from two or more 'Low' quality studies with consistent findings or evidence from a single 'Moderate' quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention."

American College of Radiology

Evidence and consensus-based appropriateness criteria from the American College of Radiology are summarized in Table 8.

Table 8. Appropriateness Criteria for Miscellaneous Indications of FDG-PET/CT

Appropriateness Criteria	Last Reviewed	FDG-PET/CT Criteria
Suspected osteomyelitis, septic arthritis, or soft tissue infection (excluding spine and diabetic foot)	2022	• May be appropriate for suspected osteomyelitis; may be appropriate for suspected osteomyelitis or soft tissue infection with implanted extra-articular surgical hardware; may be appropriate for suspected septic arthritis with arthroplasty or other implanted intra-articular surgical hardware.
Movement Disorders and Neurodegenerative Diseases	2019	May be appropriate as initial imaging for rapidly progressive dementia, suspected CJD; usually not appropriate for chorea, suspected HD; may be appropriate for initial imaging of parkinsonian syndromes; usually not appropriate for initial imaging of suspected neurodegeneration with brain iron accumulation; usually not appropriate for initial imaging of suspected motor neuron disease
Diagnosis of dementia	2001, reaffirmed 2004	PET imaging not recommended for routine use in diagnostic evaluation of dementia (LOR: moderate clinical certainty)
Early detection of dementia	2001, reaffirmed 2003, 2015	Not addressed
Diagnosis of new onset-PD	2006: reaffirmed 2013; retired 2016	Evidence insufficient to support or refute FDG-PET as a means of distinguishing PD from other parkinsonian syndromes
Evaluation of depression, psychosis, and dementia in PD	2006	Not addressed
Dementia and movement disorders	2016	May be appropriate in patients with possible or probable AD and to differentiate suspected FTD, LBD, CJD, or vascular dementia; usually not appropriate in patients with suspected HD, clinical features of PD or hemochromatosis, or motoneuron disease
Imaging after total knee arthroplasty	2017	Usually not appropriate for routine follow-up of asymptomatic patient, in work-up for suspected periprosthetic infection, or for evaluation of prosthetic loosening
Seizures and epilepsy	2014	Usually appropriate for surgical planning in medically refractory epilepsy; may be appropriate for new-onset seizure unrelated to trauma in adults (age ≥18 y) and for posttraumatic (subacute or chronic), new-onset seizure; otherwise, usually not appropriate for new-onset seizure
Crohn disease	2014	Usually not appropriate

Fever without source - child	2015	May be appropriate. This procedure should not be used as the initial study. Consider if extensive clinical and imaging work-up is negative.
Suspected osteomyelitis of the foot in patients with DM	2012; revised 2019	Usually not appropriate for initial imaging. May be appropriate for soft tissue swelling with or without ulcer, suspected osteomyelitis or early neuropathic arthropathy changes of the foot in patients with DM, suspected osteomyelitis of the foot in patients with DM with or without neuropathic arthropathy, and additional imaging following radiographs.
Noncerebral Vasculitis	2021	Usually appropriate for initial imaging of suspected LVV (FDG-PET/CT). Usually not appropriate for initial imaging of suspected medium vessel vasculitis.

AD: Alzheimer disease; CJD: Creutzfeldt-Jakob disease; CT: computed tomography; DM: diabetes mellitus; FDG: fluorine 18 fluorodeoxyglucose; FTD: frontotemporal dementia; HD: Huntington disease; LBD: Lewy body disease; LOR: level of recommendation; LVV: large vessel vasculitis; PD: Parkinson disease; PET: positron emission tomography.

Infectious Diseases Society of America

The Infection Diseases Society of America (IDSA) and the Pediatric Infectious Diseases Society (2021) published an evidence-based guidelines on acute hematogenous osteomyelitis in children.(73) Studies that validate the utility of FDG-PET for diagnosing pediatric osteomyelitis were listed as a future research need.

The Infectious Diseases Society of America (2015) published evidence-based, consensus guidelines on the diagnosis and treatment of native vertebral osteomyelitis in adults.(74) The guidelines stated that PET "is highly sensitive for detecting chronic osteomyelitis. A negative PET scan excludes the diagnosis of osteomyelitis, including native vertebral osteomyelitis, as the sensitivity of the test is expected to be very high in view of the high concentration of red marrow in the axial skeleton."

IDSA (2013) published evidence-based, consensus guidelines on the diagnosis and management of prosthetic joint infections.(75) The guidelines concluded that PET should not be routinely used to diagnoses prosthetic joint infection (Strength of recommendation: B [based on moderate evidence; Quality of evidence: III [expert opinion and descriptive studies]).

IDSA (2012) published evidence-based, consensus guidelines on the diagnosis and treatment of diabetic foot infections.(76) The guidelines concluded that the role of FDG-PET in evaluating a diabetic foot infection has not been established.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Currently, unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00811122	Biodistribution of 11C-PIB PET in Alzheimer's Disease, Frontotemporal Dementia, and Cognitively Normal Elderly	30	Apr 2022
NCT05000138	FDG Digital PET/CT as First Line Investigation for Giant Cell Arteritis	134	Mar 2023
NCT05009563	Evaluation of COVID-19 by Whole-body FDG-PET/CT	50	Jan 2022
NCT00194298	FDG-PET Imaging in Complicated Diabetic Foot	240	Jan 2020
Unpublished			

NCT04154215	FDG Metabolism in Dementia with Lewy Body (DLB) Patients as Indicated by PET Dynamic Acquisition	100	Dec 2021
NCT04725162	Epileptogenic Focus Localization for Children with Epilepsy Using 18F-FDG PET Molecular Imaging	234	Jun 2021
NCT03022968	Tau Brain Imaging in Typical and Atypical Alzheimer's Disease	24	Nov 2019
NCT00329706	Early and Long-Term Value of Imaging Brain Metabolism	710	Jan 2017 (completed)

NCT: national clinical trial

Government Regulations
National:

FDG PET for Refractory Seizures (220.6.9) Implementation Date 4/18/05
Medicare covers FDG-PET for pre-surgical evaluation for the purpose of localization of a focus of refractory seizure activity.

Limitations: Covered only for pre-surgical evaluation.

FDG-PET for Dementia and Neurodegenerative Diseases (CAG-00088N); (220.6.13)
Implemented 10/30/09

> "Medicare covers FDG-PET scans for either the differential diagnosis of fronto-temporal dementia (FTD) and Alzheimer's disease (AD) under specific requirements; OR, its use in a Centers for Medicare & Medicaid Services (CMS)-approved practical clinical trial focused on the utility of FDG-PET in the diagnosis or treatment of dementing neurodegenerative diseases".(83)

Specific requirements for each indication are clarified in the document.

Nationally Covered Indications

1. FDG-PET Requirements for Coverage in the Differential Diagnosis of AD and FTD:

   An FDG-PET scan is considered reasonable and necessary in patients with a recent diagnosis of dementia and documented cognitive decline of at least 6 months, who meet diagnostic criteria for both AD and FTD. These patients have been evaluated for specific alternate neurodegenerative diseases or other causative factors, but the cause of the clinical symptoms remains uncertain.

   The following additional conditions must be met before an FDG-PET scan will be covered:
   a. The patient's onset, clinical presentation, or course of cognitive impairment is such that FTD is suspected as an alternative neurodegenerative cause of the cognitive decline. Specifically, symptoms such as social disinhibition, awkwardness, difficulties with language, or loss of executive function are more prominent early in the course of FTD than the memory loss typical of AD;
   b. The patient has had a comprehensive clinical evaluation (as defined by the American Academy of Neurology (AAN)) encompassing a medical history from the patient and a well-acquainted informant (including assessment of activities of daily living), physical and mental status examination (including formal documentation of cognitive decline occurring over at least 6 months) aided by cognitive scales or neuropsychological

testing, laboratory tests, and structural imaging such as magnetic resonance imaging (MRI) or computed tomography (CT);

c. The evaluation of the patient has been conducted by a physician experienced in the diagnosis and assessment of dementia;
d. The evaluation of the patient did not clearly determine a specific neurodegenerative disease or other cause for the clinical symptoms, and information available through FDG-PET is reasonably expected to help clarify the diagnosis between FTD and AD and help guide future treatment;
e. The FDG-PET scan is performed in a facility that has all the accreditation necessary to operate nuclear medicine equipment. The reading of the scan should be done by an expert in nuclear medicine, radiology, neurology, or psychiatry, with experience interpreting such scans in the presence of dementia;
f. A brain single photon emission computed tomography (SPECT) or FDG-PET scan has not been obtained for the same indication.
    - The indication can be considered to be different in patients who exhibit important changes in scope or severity of cognitive decline, and meet all other qualifying criteria listed above and below (including the judgment that the likely diagnosis remains uncertain). The results of a prior SPECT or FDG-PET scan must have been inconclusive or, in the case of SPECT, difficult to interpret due to immature or inadequate technology. In these instances, an FDG-PET scan may be covered after one year has passed from the time the first SPECT or FDG-PET scan was performed.
g. The referring and billing provider(s) have documented the appropriate evaluation of the Medicare beneficiary. Providers should establish the medical necessity of an FDG-PET scan by ensuring that the following information has been collected and is maintained in the beneficiary medical record:
    - Date of onset of symptoms;
    - Diagnosis of clinical syndrome (normal aging; mild cognitive impairment or MCI; mild, moderate or severe dementia);
    - Mini mental status exam (MMSE) or similar test score;
    - Presumptive cause (possible, probable, uncertain AD);
    - Any neuropsychological testing performed;
    - Results of any structural imaging (MRI or CT) performed;
    - Relevant laboratory tests (B12, thyroid hormone); and,
    - Number and name of prescribed medications.

The billing provider must furnish a copy of the FDG-PET scan result for use by CMS and its contractors upon request. These verification requirements are consistent with federal requirements set forth in 42 Code of Federal Regulations section 410.32 generally for diagnostic x-ray tests, diagnostic laboratory tests, and other tests. In summary, section 410.32 requires the billing physician and the referring physician to maintain information in the medical record of each patient to demonstrate medical necessity [410.32(d) (2)] and submit the information demonstrating medical necessity to CMS and/or its agents upon request [410.32(d)(3)(I)] (OMB number 0938-0685).

2. FDG-PET Requirements for Coverage in the Context of a CMS-approved Practical Clinical Trial Utilizing a Specific Protocol to Demonstrate the Utility of FDG-PET in the Diagnosis, and Treatment of Neurodegenerative Dementing Diseases
    - An FDG-PET scan is considered reasonable and necessary in patients with mild cognitive impairment or early dementia (in clinical circumstances other than those specified in subparagraph 1) only in the context of an approved clinical trial that

contains patient safeguards and protections to ensure proper administration, use and evaluation of the FDG-PET scan.

- The clinical trial must compare patients who do and do not receive an FDG-PET scan and have as its goal to monitor, evaluate, and improve clinical outcomes. In addition, it must meet the following basic criteria:
  a. Written protocol on file;
  b. Institutional Review Board review and approval;
  c. Scientific review and approval by two or more qualified individuals who are not part of the research team; and,
  d. Certification that investigators have not been disqualified.

<u>FDG-PET for Infection and Inflammation</u> (220.6.16) Implementation Date 6/22/21
Effective January 1, 2021, the Centers for Medicare & Medicaid Services determined that no national coverage determination (NCD) is appropriate at this time for FDG PET for Inflammation and Infection. In the absence of an NCD, coverage determinations will be made by the Medicare Administrative Contractors under section 1862(a)(1)(A) of the Social Security Act.

Local:
There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Positron Emission Tomography for Cardiac Applications
- Positron Emission Tomography Oncologic Applications

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through February, 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/13/02	11/13/02	11/13/02	Joint policy established
3/1/07	12/28/06	9/18/09	Routine maintenance; new diagnoses added
11/1/08	8/19/08	10/30/08	Maintenance, combined PET for brain-non-oncologic and initial diagnosis of breast cancer with this policy; added PET for myocardial indications
5/1/09	2/10/09	2/10/09	Maintenance, initial diagnosis of breast cancer added as investigational to PET scan policy
9/1/09	6/16/09	6/16/09	Redefined criteria for PET myocardial perfusion
7/1/11	4/19/11	5/3/11	Additional references added. Clarified indications for PET for oncologic conditions.
1/1/12	10/11/11	11/9/11	Joint policy established; separated “PET Scans for Miscellaneous Conditions” policy from combined joint policy “PET Scans” to mirror BCBSA policy. See prior history below.
5/1/14	2/18/14	3/3/14	Routine maintenance: • Removed procedure codes A9526, A9552, and A9580. • Added inflammatory bowel disease as experimental/investigational indications. • Added “Non-cardiac, non-oncologic” to policy title. • Updated description, rationale and references. • Clarified description of type of seizures qualifying for PET scan as a diagnostic tool.

9/1/15	6/16/15	7/16/15	Routine maintenance • Updated criteria: Vascular prosthetic graft infection, sarcoidosis, fever of unknown origin, and inflammation of unknown origin added as investigational indications. Acanthocytosis and assessment of cerebral blood flow in newborns revise, but no change to intent. • References and rationale updated.
9/1/16	6/21/16	6/21/16	Routine maintenance
9/1/17	6/20/17	6/20/17	Routine maintenance Added "Fluorodeoxyglucose F 18" to policy title Added procedure code A9552
9/1/18	6/19/18	6/19/18	• Routine maintenance • Codes added – 78814, 78815, 78816 • Title simplified to maintain coordination with other PET scan policies
7/1/19	4/16/19		• Routine maintenance
7/1/20	4/14/20		• Routine maintenance
7/1/21	4/20/21		• Routine maintenance
7/1/22	4/19/22		• Routine maintenance • Cover PET for differentiation of FTD vs Alzheimer's disease
7/1/23	4/18/23		• Routine maintenance • Added codes: A9601 eff 7/1/22 and A9602 eff 10/1/22 as E/I per code update. • BCBSA updated policy 6.01.06 - Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography on 10/13/22. • BCBSA transferred Alzheimer and dementia information and criteria to PET for eval of

			Alzheimer disease on 9/9/21 to policy 6.01.55 - Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease, last updated on 10/13/22. Determination made at 4/19/21 JUMP to keep dementia and Alzheimer's information in this policy o This JUMP policy discusses only PET with fluorine 18 fluorodeoxyglucose whereas the BCBSA Alzheimer policy addresses beta-amyloid as well (all EI) • Vendor: Carelon. Carelon covers: o PET when used to distinguish between frontotemporal dementia (FTD) and Alzheimer's ▪ Inclusion added • In line with Medicare • Diverges with BCBSA – EI (ky)

Next Review Date: 2nd Qtr, 2024

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: 10/12/98	Revised: 5/8/01, 1/4/02
BCBSM: 10/30/00	Revised: 12/4/00

Blue Care Network Benefit Coverage
Policy: Positron Emission Tomography (PET) for Miscellaneous Applications (Non-cardiac, non-oncologic)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.