Medical Policy

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Title: Positron Emission Tomography (PET) Scanning: Miscellaneous (Non-cardiac, Non-Oncologic) Applications of Fluorine 18 Fluorodeoxyglucose

Related Policies:	▪ *PET Scanning: Cardiac Applications* ▪ *PET Scanning: In Oncology to Detect Early Response during Treatment* ▪ *PET Scanning: Oncologic Applications*

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Populations	Interventions	Comparators	Outcomes
Individuals: • With epileptic seizures who are candidates for surgery	Interventions of interest are: • Fluorine 18 fluorodeoxyglucose positron emission tomography	Comparators of interest are: • Ictal scalp electroencephalography • Magnetic resonance imaging	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life • Hospitalizations • Medication use • Resource utilization

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected chronic osteomyelitis	Interventions of interest are: • Fluorine 18 fluorodeoxyglucose positron emission tomography	Comparators of interest are: • Computed tomography • Plain radiograph • Magnetic resonance imaging	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Change in disease status • Functional outcomes • Quality of life • Hospitalizations
Individuals: • With suspected large vessel vasculitis	Interventions of interest are: • Fluorine 18 fluorodeoxyglucose positron emission tomography	Comparators of interest are: • Clinical diagnosis without fluorine 18 fluorodeoxyglucose positron emission tomography	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Symptoms • Morbid events • Quality of life • Hospitalizations • Treatment-related morbidity
Individuals: • With diverse noncardiac or nononcologic conditions (e.g., central nervous system, pulmonary, and musculoskeletal diseases)	Interventions of interest are: • Fluorine 18 fluorodeoxyglucose positron emission tomography	Comparators of interest are: • Computed tomography • Plain radiograph • Magnetic resonance imaging	Relevant outcomes include: • Overall survival • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life • Hospitalizations • Medication use • Resource utilization

DESCRIPTION

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

OBJECTIVE

The objective of this evidence review is to determine whether use of fluorine 18 fluorodeoxyglucose positron emission tomography improves the net health outcome in individuals with epilepsy, suspected chronic osteomyelitis, suspected large vessel vasculitis, and other noncardiac and nononcologic conditions (e.g., central nervous system, pulmonary, and musculoskeletal diseases).

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 2 high-energy photons in opposite directions that can be simultaneously detected (referred to as *coincidence detection*) by a PET scanner, which comprises multiple stationary detectors that encircle the region of interest.

A variety of tracers are used for PET scanning, including oxygen 15, nitrogen 13, carbon 11, and fluorine 18. 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 the 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 the FDA for use as diagnostic imaging agents. These radiopharmaceuticals are approved for specific conditions.

In December 2009, the FDA issued guidance for Current Good Manufacturing Practices for PET drug manufacturers.[1] and, in August 2011, issued similar Current Good Manufacturing Practices guidance for small businesses compounding radiopharmaceuticals.[2] 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 FDA through the 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]

POLICY

A. Positron emission tomography (PET) using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) may be considered **medically necessary** in:
   1. The assessment of selected individuals with epileptic seizures who are candidates for surgery (see Policy Guidelines)
   2. The diagnosis of chronic osteomyelitis

B. The use of FDG-PET for all other miscellaneous indications is **experimental / investigational** including but not limited to:
   1. Central Nervous System Diseases
      a. Autoimmune disorders with central nervous system (CNS) manifestations, including:
         i. Behçet syndrome
         ii. lupus erythematosus
      b. Cerebrovascular diseases, including:
         i. arterial occlusive disease (arteriosclerosis, atherosclerosis)
         ii. carotid artery disease
         iii. cerebral aneurysm
         iv. cerebrovascular malformations (arteriovenous malformation and Moya-Moya disease)
         v. hemorrhage
         vi. infarct
         vii. ischemia
      c. Degenerative motor neuron diseases, including:
         i. amyotrophic lateral sclerosis
         ii. Friedreich ataxia
         iii. olivopontocerebellar atrophy
         iv. Parkinson disease
         v. progressive supranuclear palsy
         vi. Shy-Drager syndrome
         vii. spinocerebellar degeneration
         viii. Steele-Richardson-Olszewski syndrome
         ix. Tourette syndrome
      d. Demyelinating diseases, such as multiple sclerosis
      e. Developmental, congenital, or inherited disorders, including:
         i. adrenoleukodystrophy
         ii. Down syndrome
         iii. Huntington chorea
         iv. kinky-hair disease (Menkes disease)
         v. Sturge-Weber syndrome (encephalofacial angiomatosis) and the phakomatoses
      f. Miscellaneous
         i. chronic fatigue syndrome
         ii. sick building syndrome
         iii. posttraumatic stress disorder
      g. Nutritional or metabolic diseases and disorders, including:
         i. acanthocytosis

- ii. hepatic encephalopathy
- iii. hepatolenticular degeneration
- iv. metachromatic leukodystrophy
- v. mitochondrial disease
- vi. subacute necrotizing encephalomyelopathy

h. Psychiatric diseases and disorders, including:
- i. affective disorders
- ii. depression
- iii. obsessive-compulsive disorder
- iv. psychomotor disorders
- v. schizophrenia

i. Pyogenic infections, including:
- i. aspergillosis
- ii. encephalitis

j. Substance abuse, including the central nervous system effects of alcohol, cocaine, and heroin

k. Trauma, including brain injury and carbon monoxide poisoning

l. Viral infections, including:
- i. HIV / AIDS
- ii. AIDS dementia complex
- iii. Creutzfeldt-Jakob syndrome
- iv. progressive multifocal leukoencephalopathy
- v. progressive rubella encephalopathy
- vi. subacute sclerosing panencephalitis

m. Mycobacterium infection

n. Migraine

o. Anorexia nervosa

p. Assessment of cerebral blood flow in newborns
- i. Vegetative vs locked-in syndrome

2. Pulmonary Diseases
   - a. Adult respiratory distress syndrome
   - b. Diffuse panbronchiolitis
   - c. Emphysema
   - d. Obstructive lung disease
   - e. Pneumonia

3. Musculoskeletal Diseases
   - a. Spondylodiscitis
   - b. Joint replacement follow-up

4. Other
   - a. Giant cell arteritis
   - b. Vasculitis
   - c. Vascular prosthetic graft infection
   - d. Inflammatory bowel disease
   - e. Sarcoidosis
   - f. Fever of unknown origin
   - g. Inflammation of unknown origin

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.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 19, 2024.

This review was informed in part by 3 TEC Assessments (1996) that addressed various applications of positron emission tomography (PET).[5,6,7,]

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

INTRACTABLE EPILEPSY

Clinical Context and Test Purpose

The purpose of fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) in individuals with epilepsy is to inform the decision on selecting treatment regimens.

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

Populations
The population of interest is patients with intractable epilepsy who are candidates for surgery.

Approximately one-third of patients with epilepsy do not achieve adequate seizure control with antiepileptic drugs.[8,8,] 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.

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

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.[5] 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 Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography for Epilepsy

Study	Dates	Trials	N (Range)	Design	Duration
Courtney et al (2024)[11]	1993-2022	98	4104	NR	12 to 60 months
Niu et al (2021)[12]	1995-2020	44	2246 (6 to 194)	NR	NR
Jones et al (2016)[13]	1946-2014	27	3163 (25 to 434)	OBS	>1 year
Wang et al (2016)[14]	2000-2015	18	391 (5 to 86)	NR	1 to 6.5 years
Burneo et al (2015)[15]	1946-2013	39	2650	OBS	1 year, median
Englot et al (2012)[16]	1990-2010	21[a]	1199 (13 to 253)[a]	OBS	>4 years
Willmann et al (2007)[17]	1992-2006	46	1112 (2 to 117)	OBS	3 to 144 months

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

Courtney et al (2024) conducted a meta-analysis of studies that described the association of localized hypometabolism seen on FDG-PET and outcome of epilepsy surgery.[11] Included studies had to report surgical outcome at least 12 months after surgery. The odds of achieving a favorable outcome (i.e., Engel class I, International League Against Epilepsy class 1 or 2, or seizure-free) after surgery (as determined by a random-effects analysis) was 2.68 (95% confidence interval [CI], 2.08 to 3.45) with localizing FDG-PET hypometabolism. Results were similar in patients with and without an epileptogenic lesion detected on MRI. Diffuse FDG-PET hypometabolism was associated with unfavorable outcomes (odds ratio [OR], 0.34; 95% CI, 0.22 to 0.54).

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.[12] 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}F-FDG-PET. Results are summarized in Table 2. Pooled sensitivity and specificity of FDG-PET were 0.66 (95% 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.[13] 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 databases. Twenty-seven studies with 3163 patients were included in the review, of which 11 observational studies with 1358 patients 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.[14] 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% 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.[15] The literature review included searches of the PubMed, EMBASE, 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; ranges are provided in Table 2.

Englot et al (2012) performed a systematic 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.[16] 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. 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 that included 46 studies identified through a PubMed search.[17] 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 (PPV) for ipsilateral PET hypometabolism was calculated but the reviewers noted a 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% (Table 2). The incremental benefit 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
Courtney et al (2024)[11,]	98	4104	Surgical outcome	OR of favorable outcome when localizing FDG-PET hypometabolism was identified, 2.68	2.08 to 3.45	30.89%	NR
Niu et al (2021)[12,]	44	2246	Concordance with reference standard (EEG or surgical outcome)	Pooled concordance (overall), 0.67	0.60 to 0.73	90.5%	.00
Jones et al (2016)[13,]	11	1358	Surgical outcome	• No overall summary given • Reported conflicting findings on prognostic importance of PET-identified focal hypometabolism	No pooling	NR	NR
Wang et al (2016)[14,]	5	NR	Surgical outcome (freedom from seizures)	OR for PET hypometabolism positive vs. negative, 2.11	0.95 to 4.65	0	.06
Burneo et al (2015)[15,]	8	310	Percent agreement, localization with PET vs. EEG	• 56% to 90% overall (adults) • 63% to 90% in temporal lobe epilepsy (adults)	No pooling	NR	NR
	13	1064	Prognostic accuracy (good surgical outcome)	36% to 89% (adults)	No pooling	NR	NR
	6	690	Clinical decisions (influence decision making)	• 53% to 71% (adults) • 51% to 95% (children)	No pooling	NR	NR
Englot et al (2012)[16,]	21[a]	1199[a]	Prognostic accuracy (good	% for PET focal vs. PET nonfocal, 52% vs. 48%	NR	NR	.61

Study	Studies	N	Outcomes	Estimate or Range	95% CI	I^2	p
			surgical outcome)				
Willmann et al (2007)[17]	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).[18] 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 postsurgery, 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, 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 3 retrospective studies on change in clinical management based on FDG-PET results in children with epilepsy.[15] After receiving FDG-PET results on adults, some clinicians changed surgical decisions, used the results to guide intracranial EEG, and ruled out 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 the 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 the results were 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 are 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 individuals with chronic osteomyelitis is to confirm a diagnosis or to inform the decision on selecting treatment regimens.

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

Populations

The population of interest is 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.[19,] 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 CT, both of which have high sensitivity in diagnosing osteomyelitis, can be used in patients with metal hardware.[20,] 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

Computed tomography, 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 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
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

Systematic Reviews
Jin et al (2024) conducted a systematic review and meta-analysis of 9 studies that compared FDG-PET and MRI or white blood cell scintigraphy in diagnostic efficacy for food osteomyelitis in patients with diabetes.[21,] The overall sensitivity and specificity of FDG-PET was 0.83 (95% CI, 0.69 to 0.94) and 0.92 (95% CI, 0.86 to 0.97), respectively. There was no statistical difference in sensitivity and specificity between FDG-PET and MRI or white blood cell scintigraphy (all $p>.05$).

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.[22,] Various imaging techniques were included: PET, MRI, CT, x-rays, planar scintigraphy, ultrasound, and single-positron emission CT. 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.[23,] 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.[24] A meta-analysis of 4 studies found a sensitivity of 74% (95% CI, 60% to 85%), a specificity of 91% (95% CI, 85% to 96%), a positive likelihood ratio of 5.56 (95% CI, 2.02 to 15.27), a negative likelihood ratio of 0.37 (95% CI, 0.10 to 1.35), and a diagnostic odds ratio of 16.96 (95% CI, 2.06 to 139.66). The summary area under the receiver operating characteristic curve was 0.874.

Termaat et al (2005) conducted a systematic review of diagnostic imaging to assess chronic osteomyelitis.[25] 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"[26]; (2) 22 trauma patients scheduled for surgery who had suspected metallic implant-associated infection[27]; (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[28]; and (4) 30 consecutive nondiabetic patients referred for possible chronic osteomyelitis.[29] 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.[30] 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, 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, a 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 5 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.

SUSPECTED LARGE VESSEL VASCULITIS

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

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

Populations
The population of interest includes patients with suspected LVV.

Large vessel vasculitis causes granulomatous inflammation primarily of the aorta and its major branches.[31] There are 2 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.[32,33] The definitions have since been refined by the International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides (2012).[34] 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.[35] 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
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
Summaries of characteristics and results of several meta-analyses of FDG-PET that have been published on the diagnosis and management of LVV are shown in Tables 3 and 4 and are briefly described below.

Table 3. Characteristics of Systematic Reviews on Use of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography for Large Vessel Vasculitis

Study	Dates	Studies	N (Range)	Design	Outcomes
Gonzalez-Garcia et al (2024)[36,]	2018-2022	17	1042 (19 to 84)	OBS	Prevalence of extracranial LVV
van der Geest et al (2021)[37,]	1987-2020	21	798 (11 to 112)	OBS	Diagnostic accuracy for relapsing/refractory disease
Lee et al (2016)[38,]	Up to 2015	8	400 (21 to 93)	OBS	Diagnostic accuracy for GCA and TA

Study	Dates	Studies	N (Range)	Design	Outcomes
Soussan et al (2015)[39]	2000-2013	21	712 (18 to 93)	OBS	Diagnostic accuracy for GCA; assessment of disease activity in TA
Puppo et al (2014)[40]	1999-2014	19	977 (8 to 304)	OBS	Diagnostic accuracy for GCA
Treglia et al (2011)[41]	Up to 2011	32	604	OBS	Diagnostic accuracy for GCA and TA; assessment of disease activity; monitor treatment response
Besson et al (2011)[42]	Up to 2011	14	Unclear	OBS	Diagnostic accuracy for GCA

GCA: giant cell arteritis; OBS: observational; TA: Takayasu arteritis.

A meta-analysis by Gonzalez-Garcia et al (2024) evaluated the prevalence of extracranial LVV using FDG-PET/CT in patients with GCA and polymyalgia rheumatica.[36] Seventeen studies were included in the analysis. The prevalence of extracranial LVV in patients with GCA was 60.1%, and in patients with polymyalgia rheumatica was 41.8% (p=.006). The analysis is limited by high heterogeneity, a small number of patients in each study and the use of various clinical criteria among studies as the reference standard.

A meta-analysis by van der Geest et al (2021) evaluated the diagnostic accuracy of FDG-PET/CT for monitoring LVV treatment response.[37] 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 and PET/CT for LVV.[38] The search included studies indexed in PubMed, EMBASE or the Cochrane Library that used the ACR classification system as the reference standard diagnosis. Eight studies (N=400 participants) were identified for inclusion. Five studies included participants with both GCA and 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 4. Interpretation of these results was 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 3 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.[39] 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 4 cases included. The sensitivity and specificity of FDG-PET for the diagnosis of large-vessel inflammation were calculated from each selected study and then pooled for meta-analysis with a random-effects model. Disease activity was assessed with the National Institutes of Health Stroke Scale[43] 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 greater than the liver uptake differed significantly between GCA plus TA patients and controls ($p<.001$). A summary of the results is shown in Table 4. 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 greater than the liver uptake appears to be a good criterion for diagnosing vascular inflammation, further studies would be 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.[40] 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, 6 used semiquantitative criteria, and 3 used both. Meta-analyses were not performed. Overall, qualitative methods were more specific but less sensitive, than semiquantitative methods. Diagnostic performance varied by vessel and by thresholds (cutoffs) for positivity. Results are shown in Table 4.

Treglia et al (2011) published a systematic review of PET and PET/CT in patients with LVV.[41] 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, the extent of disease, response to therapy, and prediction of relapse or complications. Reviewers did not pool findings. The authors 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 to assess use of FDG-PET for patients with suspected GCA; reviewers searched the PubMed, EMBASE, and the Cochrane databases.[42] Studies were included if they evaluated the performance of FDG-PET for the diagnosis of GCA, had at least 8 participants, used ACR criteria as the reference standard to confirm diagnosis of GCA, and included a control group. Fourteen studies were identified; 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, PPV, NPV, positive and negative likelihood ratio, and diagnostic accuracy using a random-effects model. Results are shown in Table 4. There was statistically significant between-study heterogeneity for sensitivity, PPV, and NPV. All studies in the meta-analysis were small case-control studies.

Table 4. Results of Systematic Reviews Assessing Use of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography for Large Vessel Vasculitis

Study	Studies	N	Outcomes	Estimate (95% CI)
Gonzalez-Garcia et al (2024)[36,]	17	1042	Prevalence of extracranial LVV as assessed by FDG-PET	• Patients with GCA: 60.1% (44.2% to 74.9%) • Patients with polymyalgia rheumatica: 41.8% (26.7% to 57.8%)
van der Geest et al (2021)[37,]	21	798	Diagnostic accuracy of FDG-PET/CT for relapsing/refractory disease	• Sensitivity: 77% (57% to 90%) • Specificity: 71% (47% to 87%) • PLR: 2.65 (1.16 to 6.08) • NLR: 0.32 (0.13 to 0.80)
Lee et al (2016)[38,]	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)[39,]	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)[40,]	10	633	Diagnostic accuracy for GCA	• Sensitivity range: 56% to 77% • Specificity range: 77% to 100% • PPV range: 93% to 100% • NPV range: 70% to 82%
•	6	282	Diagnostic accuracy for GCA	• Sensitivity range: 58% to 90%

Study	Studies	N	Outcomes	Estimate (95% CI)
				• Specificity range: 42% to 95% • PPV range: 79% to 89% • NPV range: 95% to 98%
•	3	72	Diagnostic accuracy for GCA	• Sensitivity range: 65% to 100% • Specificity range: 45% to 100%
Treglia et al (2011)[41,]	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)[42,]	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.[44,] 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% CI.

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, 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 included were small, many lacked controls, and all 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 individuals with diverse noncardiac or nononcologic conditions is to confirm a diagnosis or to inform the decision on selecting treatment regimens.
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
Computed tomography, 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
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

Systematic Reviews
Numerous systematic reviews have described the use of PET in patients with carotid stenosis[45,]; inflammatory diseases[46,47,48,49,50,]; fever of unknown origin[51,52,53,54,55,]; hyperinsulinemic hypoglycemia[56,57,]; spondylodiscitis[58,]; spinal infection[59,]; mycobacterium infection[60,61,]; Creutzfeldt-Jakob disease[62,]; vascular prosthetic graft infection[63,64,65,]; prosthetic infection after knee or hip arthroplasty[66,67,]; inflammatory bowel disease[68,][Lin CY, Chang MC, Kao CH. Comparing the Diagnostic.... ed. Jul 08 2024. PMID 38973081]; atypical parkinsonism[70,]; and Huntington disease.[71,] 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 improve 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, 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 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 have compared PET with other diagnostic modalities and no studies have reported on patient clinical outcomes.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[72,] The AAOS recommendation regarding fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) is that there is limited strength of evidence supporting the use of FDG-PET/computed tomography (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 2 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 5.

Table 5. Appropriateness Criteria for Miscellaneous Indications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

Appropriateness Criteria	Last Reviewed	FDG-PET/CT Criteria
Suspected osteomyelitis, septic arthritis, or soft tissue infection (excluding spine and diabetic foot)[73,]	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[74,]	2019	May be appropriate as initial imaging for rapidly progressive dementia, suspected CJD; usually not appropriate for chorea, suspected HD; may be

Appropriateness Criteria	**Last Reviewed**	**FDG-PET/CT Criteria**
		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
Dementia and movement disorders[75,]	2016; revised 2019	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[74,]	2023	Usually not appropriate for routine follow-up of asymptomatic patients, in work-up for suspected periprosthetic infection, for evaluation of prosthetic loosening, or suspected periprosthetic or hardware fracture
Seizures and epilepsy[76,]	2014; revised 2019	Usually appropriate for surgical planning in known seizure disorder; usually not appropriate for new-onset seizure, whether unrelated to trauma or with a history of trauma; may be appropriate (disagreement) for known seizure disorder with unchanged seizure semiology; may be appropriate for known seizure disorder with change in seizure semiology or new neurologic deficit or no return to previous neurologic baseline; may be appropriate (disagreement) for known seizure disorder with a history of trauma
Crohn disease[77,]	2014; revised 2019	Usually not appropriate
Fever without source - child[74,]	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[78,]	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[79,]	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; LVV: large vessel vasculitis; PD: Parkinson disease; PET: positron emission tomography.

Infectious Diseases Society of America

The Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (2023) published a guideline on the treatment of diabetes-related foot infections.[80] The guideline recommends magnetic resonance imaging (MRI) if the diagnosis of diabetes-related osteomyelitis needs to be confirmed, but PET is recommended as an alternative to MRI (conditional recommendation, low quality of evidence). The supporting text cites evidence regarding the high specificity of FDG-PET in this setting.

The IDSA and the Pediatric Infectious Diseases Society (2021) published an evidence-based guidelines on acute hematogenous osteomyelitis in children.[81] Studies that validate the utility of FDG-PET for diagnosing pediatric osteomyelitis were listed as a future research need.

The IDSA (2015) published evidence-based, consensus guidelines on the diagnosis and treatment of native vertebral osteomyelitis in adults.[82] 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."

The IDSA (2013) published evidence-based, consensus guidelines on the diagnosis and management of prosthetic joint infections.[83] The guidelines concluded that PET should not be routinely used to diagnose prosthetic joint infection (strength of recommendation: B [based on moderate evidence]; quality of evidence: III [expert opinion and descriptive studies]). These guidelines have now been archived and replaced by an endorsement of the clinical practice guidelines on the diagnosis and prevention of periprosthetic joint infections issued by AAOS (2019) described above.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Currently ongoing and unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06558357	Evaluation of the Diagnostic Performance of 18-FDG PET-CT Scores for the Diagnosis of Polymyalgia Rheumatica and Comparison With Others Inflammatory Rheumatic Diseases	210	Dec 2024
NCT06019975	FDG-PET in the Diagnosis of Autoimmune Encephalitis	90	Apr 2024
NCT05000138	FDG Digital PET/CT as First Line Investigation for Giant Cell Arteritis	134	Jun 2025
NCT05009563	Evaluation of COVID-19 by Whole-body FDG-PET/CT	50	Jan 2022 (unknown status)

NCT No.	**Trial Name**	**Planned Enrollment**	**Completion Date**
NCT00194298	FDG-PET Imaging in Complicated Diabetic Foot	240	Feb 2025
Unpublished			
NCT02084147	PET-MRI: Evaluation, Optimization and Clinical Implementation	72	Oct 2018 (completed)

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
78608	Brain imaging, positron emission tomography (PET); metabolic evaluation
78609	Brain imaging, positron emission tomography (PET); perfusion evaluation
78811	Positron emission tomography (PET) imaging; limited area (e.g., chest, head/neck)
78812	Positron emission tomography (PET) imaging; skull base to mid-thigh
78813	Positron emission tomography (PET) imaging; whole body
78814	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; limited area (e.g., chest, head/neck)
78815	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; skull base to mid-thigh
78816	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; whole body
A9552	Fluorodeoxyglucose F-18 FDG, diagnostic, per study dose, up to 45 millicuries
G0235	PET imaging, any site, not otherwise specified

REVISONS	
10-30-2013	Miscellaneous (Non-cardiac, Non-oncologic) Applications of PET Scanning was originally part of the Positron Emission Tomography (PET) medical policy. Miscellaneous (Non-cardiac, Non-oncologic) Applications of PET Scanning was separated out and placed into a separate medical policy, Positron Emission Tomography (PET) Scanning: Miscellaneous (Non-cardiac, Non-oncologic) Applications. The medical policy language was unchanged.
	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis codes *(Effective October 1,2014)*
	Updated Reference section.
12-31-2013	In Coding section: ▪ Added HCPCS code A9599 *(Effective January 1, 2014)*
10-22-2015	Description section updated
	In Policy section: ▪ In Item B added the following indications to the experimental / investigational list:

REVISONS	
	" Central Nervous System Diseases 1. Autoimmune disorders with central nervous system (CNS) manifestations, including: a. Behçet syndrome b. lupus erythematosus 2. Cerebrovascular diseases, including: a. arterial occlusive disease (arteriosclerosis, atherosclerosis) b. carotid artery disease c. cerebral aneurysm d. cerebrovascular malformations (arteriovenous malformation and Moya-Moya disease) e. hemorrhage f. infarct g. ischemia 3. a. amyotrophic lateral sclerosis e. progressive supranuclear palsy f. Shy-Drager syndrome g. spinocerebellar degeneration h. Steele-Richardson-Olszewski syndrome i. Tourette syndrome 6. Developmental, congenital, or inherited disorders, including: a. adrenoleukodystrophy b. Down syndrome c. Huntington's chorea d. kinky-hair disease (Menkes disease) e. Sturge-Weber syndrome (encephalofacial angiomatosis) and the phakomatoses 7. Miscellaneous a. chronic fatigue syndrome b. sick building syndrome c. posttraumatic stress disorder 8. Nutritional or metabolic diseases and disorders, including: a. acanthocytosis b. hepatic encephalopathy c. hepatolenticular degeneration d. metachromatic leukodystrophy e. mitochondrial disease f. subacute necrotizing encephalomyelopathy 9. a. affective disorders b. depression c. obsessive-compulsive disorder d. psychomotor disorders e. schizophrenia 10. a. aspergillosis b. encephalitis 11. Substance abuse, including the CNS effects of alcohol, cocaine, and heroin 12. Trauma, including brain injury and carbon monoxide poisoning 14. Mycobacterium infection 15. Migraine 16. Anorexia nervosa 17. Assessment of cerebral blood flow in newborns a. Vegetative versus "locked-in" state Pulmonary Diseases 18. Adult respiratory distress syndrome 19. Diffuse panbronchiolitis

REVISONS	
	21. Obstructive lung disease 22. Pneumonia Musculoskeletal Diseases 23. Spondylodiscitis 24. Joint replacement follow-up Other 25. Giant cell arteritis 26. Vasculitis 27. Vascular prosthetic graft infection 28. Inflammatory bowel disease 29. Sarcoidosis 30. Fever of unknown origin 31. Inflammation of unknown origin” In Policy Guidelines: ▪ Removed "1. For this policy, PET scanning is discussed for the following 4 applications in oncology. Diagnosis refers to use of PET as part of the testing used in establishing whether or not a patient has cancer. Staging This refers to use of PET to determine the stage (extent) of the cancer at the time of diagnosis, before any treatment is given. Imaging at this time is generally to determine whether or not the cancer is localized. This may also be referred to as initial staging. Restaging This refers to imaging following treatment in 2 situations. Restaging is part of the evaluation of a patient in whom a disease recurrence is suspected based on signs and/or symptoms. Restaging also includes determining the extent of malignancy following completion of a full course of treatment. Surveillance This refers to use of imaging in asymptomatic patients (patients without objective signs or symptoms of recurrent disease). This imaging is completed 6 months or more (12 months or more for lymphoma) following completion of treatment. 2. As with any imaging technique, the medical necessity of positron emission tomography (PET) scanning depends in part on what imaging techniques are used either before or after the PET scanning. Due to its expense, PET scanning is typically considered after other techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography, provide inconclusive or discordant results. In patients with melanoma or lymphoma, PET scanning may be considered an initial imaging technique. If so, the medical necessity of subsequent imaging during the same diagnostic evaluation is unclear. Thus, PET should be considered for the medically necessary indications above only when standard imaging, such as CT or MRI, is inconclusive or not indicated."
	Rationale section updated
	In Coding section: ▪ Added coding notations.
	References updated
11-26-2018	Policy published October 26, 2018. Policy effective November 26, 2018.
	Changed title to "Positron Emission Tomography (PET) Scanning: Miscellaneous (Non-cardiac, Non-Oncologic) Applications of Fluorine 18 Fluorodeoxyglucose" from "Positron Emission Tomography (PET) Scanning: Miscellaneous (Non-cardiac, Non-Oncologic) Applications"
	Description section updated
	In Policy section: ▪ In Item B added "FDG" to read "The use of FDG-PET for all other miscellaneous indications is experimental / investigational including but not limited to:" ▪ In Item 11 revised "CNS" to "central nervous system"

REVISONS	
	▪ In Item 13 a revised "acquired immune deficiency syndrome (AIDS)" to "HIV / AIDS" ▪ In Item 17 a revised "state" to "syndrome" ▪ Updated Policy Guidelines
	Rationale section updated
	In Coding section: ▪ Nomenclature revised on CPT Codes: 78814, 78815, 78816 ▪ Removed HCPCS Codes: A9526, A9580, G0219 (Not applicable to the policy) ▪ Deleted HCPCS Code: A9599 (Termed effective 01-01-2018) ▪ Removed ICD Codes: M86.8x0, M86.8x1, M86.8x2, M86.8x3, M86.8x4, M86.8x5, M86.8x6, M86.8x7, M86.8x8, M86.8x9 ▪ Updated Coding notations.
	References updated
06-12-2020	Description section updated
	Rationale section updated
	References updated
12-02-2021	Updated Descriptions Section
	Updated Rationale Section
	Updated References Section
12-13-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed Coding Bullets o A PET scan essentially involves 3 separate activities: • manufacture of the radiopharmaceutical, which may be manufactured on site, or at a regional delivery center with delivery to the institution performing PET; • actual performance of the PET scan; and • interpretation of the results. ▪ Converted ICD-10 codes to Range (M86.311-M86.69), to include all codes within the range
	Updated References Section
11-17-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes
	Updated References Section
12-03-2024	Updated Descriptions Section
	Updated Policy Section ▪ Removed Section B.d : Dementias, including i. Alzheimer's disease ii. multi-infarct dementia iii. Pick disease iv. frontotemporal dementia v. dementia with Lewy bodies vi. presenile dementia
	Updated Rationale Section
	Updated References Section

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