Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

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

See also:
- *PET Scanning: Cardiac Applications*
- *PET Scanning: In Oncology to Detect Early Response during Treatment*
- *PET Scanning: Oncologic Applications*

Professional
Original Effective Date: October 1, 1997

Revision Date(s): October 30, 2013; December 31, 2013; October 22, 2015; November 26, 2018
Current Effective Date: November 26, 2018

Institutional
Original Effective Date: September 11, 2004
Revision Date(s): October 30, 2013; December 31, 2013; October 22, 2015; November 26, 2018
Current Effective Date: November 26, 2018

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 • Technetium 99 bone scintigraphy • Leukocyte scintigraphy • 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 Alzheimer disease	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 • 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 (eg, 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 physiological 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 by 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 Alzheimer disease, suspected large vessel vasculitis, and other noncardiac and nononcologic conditions (eg, central nervous system, pulmonary, and musculoskeletal diseases).

Background

Positron Emission Tomography

Positron emission tomography (PET) scans coupled 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.

Epilepsy

Approximately one-third of patients with epilepsy do not achieve adequate seizure control with antiepileptic drugs.[1] 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 (eg, the epileptogenic zone) and the extent to which it can be resected safely. Neuroimaging techniques, such as magnetic resonance imaging (MRI), electroencephalography (EEG), PET, single-photon emission computed tomography (SPECT), electric 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.[2] PET may be able to correctly identify the focus in patients with unclear or unremarkable MRI results or discordant MRI and EEG results that could reduce the need for invasive EEG. PET scanning may also help to predict which patients will have a favorable outcome following surgery. The Engel classification system is often used to describe the surgical outcome: class I: seizure-free (or free of disabling seizures); class II: nearly seizure-free; class III: worthwhile improvement; and class IV: no worthwhile improvement.[3]

Suspected Chronic Osteomyelitis

Diabetic foot infections cause substantial morbidity and are a frequent cause of lower-extremity amputations. Foot infections can spread to contiguous deep tissues including the bone. Diagnosis of osteomyelitis is challenging. The reference standard for diagnosis is examination of bacteria from a bone biopsy along with histologic findings of inflammation and osteonecrosis. In an open wound, another potential test for osteomyelitis is a probe-to-bone test, which involves exploring the wound for palpable bone using a sterile blunt metal probe.[4] 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, both of which have high sensitivity in diagnosing osteomyelitis, can be used in patients with metal hardware.[5] 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.

Suspected Alzheimer Disease

Definitive diagnosis of Alzheimer disease (AD) requires histopathologic examination of brain tissue obtained by biopsy or autopsy. In practice, clinical criteria based on clinical examination, neurologic and neuropsychological examinations, and interviews with informants (eg, family members or caregivers) are used to diagnose AD by excluding other diseases that can cause similar symptoms, and to distinguish AD from other forms of dementia. There are currently no cures or preventive therapies for AD. Early diagnosis might facilitate early treatment of cognitive, behavioral, and psychiatric symptoms which could perhaps delay functional deficits and improve quality of life. Early diagnosis may be crucial in the future if other therapies become available to treat or slow progression of the disease. FDG-PET can demonstrate reduction in glucose metabolism associated with dementia. These changes in metabolism are detectable years before the onset of clinical symptoms.[6] The changes typically have a characteristic pattern of hypometabolism that could be useful not only in distinguishing AD from normal aging but also from other dementias, psychiatric disorders, and cerebrovascular diseases.[7-9]

Large Vessel Vasculitis

Large vessel vasculitis causes granulomatous inflammation primarily of the aorta and its major branches.[10] There are 2 major types of large vessel vasculitis: giant cell arteritis and Takayasu arteritis. Classification criteria for giant cell arteritis and TA were developed by American College of Rheumatology in 1990.[11,12] The definitions have since been refined by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides.[13] 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.[14] 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.

This policy only addresses the use of radiotracers detected with the use of dedicated full-ring PET scanners. Radiotracers such as fluorodeoxyglucose (FDG) may be detected using single-photon emission computed tomography (SPECT) cameras, a hybrid PET/SPECT procedure that

may be referred to as FDG-SPECT or molecular coincidence detection. The use of SPECT cameras for PET radiotracers presents unique issues of diagnostic performance and is not considered in this policy.

Regulatory Status

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[15] 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.[17]

In 1994, the FDG radiotracer was originally approved by 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.

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 patients 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:

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. Degenerative motor neuron diseases, including:
   a. amyotrophic lateral sclerosis
   b. Friedreich ataxia
   c. olivopontocerebellar atrophy
   d. Parkinson disease
   e. progressive supranuclear palsy
   f. Shy-Drager syndrome
   g. spinocerebellar degeneration
   h. Steele-Richardson-Olszewski syndrome
   i. Tourette syndrome

4. Dementias, including:
   a. Alzheimer's disease
   b. multi-infarct dementia
   c. Pick disease
   d. frontotemporal dementia
   e. dementia with Lewy bodies
   f. presenile dementia

5. Demyelinating diseases, such as multiple sclerosis

6. Developmental, congenital, or inherited disorders, including:
   a. adrenoleukodystrophy
   b. Down syndrome
   c. Huntington 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. Psychiatric diseases and disorders, including:
   a. affective disorders
   b. depression
   c. obsessive-compulsive disorder
   d. psychomotor disorders
   e. schizophrenia

10. Pyogenic infections, including:
    a. aspergillosis
    b. encephalitis

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

12. Trauma, including brain injury and carbon monoxide poisoning

13. Viral infections, including:
    a. HIV / AIDS
    b. AIDS dementia complex
    c. Creutzfeldt-Jakob syndrome
    d. progressive multifocal leukoencephalopathy
    e. progressive rubella encephalopathy
    f. subacute sclerosing panencephalitis

14. Mycobacterium infection

15. Migraine

16. Anorexia nervosa

17. Assessment of cerebral blood flow in newborns
    a. Vegetative vs locked-in syndrome

Pulmonary Diseases

18. Adult respiratory distress syndrome
19. Diffuse panbronchiolitis
20. Emphysema
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

Policy Guidelines

In patients with epileptic seizures, appropriate candidates are patients with complex partial seizures that 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 policy, 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 PET

examination should be to avoid subjecting the patient to extended preoperative electroencephalographic recording with implanted electrodes, or to help localize and minimize the number of sites for implanted electrodes to reduce the morbidity of that procedure.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through July 10, 2018. This review was informed in part by on 3 TEC Assessments (1996) that addressed various applications of positron emission tomography (PET).[19-21]

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.

Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography

Clinical Context and Test Purpose

The purpose of fluorine 18 fluorodeoxyglucose PET (FDG-PET) in patients with epilepsy, chronic osteomyelitis, suspected Alzheimer disease (AD), suspected large vessel vasculitis (LVV), or other 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 epilepsy, chronic osteomyelitis, suspected AD, suspected LVV, or other noncardiac or nononcologic conditions?

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

Patients

The populations of interest include patients with epilepsy, chronic osteomyelitis, suspected AD, suspected LVV, or other noncardiac or nononcologic conditions (eg, central nervous system, pulmonary, and musculoskeletal diseases).

Interventions

The intervention of interest is FDG-PET.

Comparators
The following tests and practices are currently being used to make decisions about managing the following indications:

- For epilepsy, ictal scalp electroencephalography and magnetic resonance imaging (MRI).
- For suspected chronic osteomyelitis, computed tomography (CT), radiography, technetium 99 bone scintigraphy, leukocyte scintigraphy, and MRI.
- For suspected AD, clinical diagnosis without FDG-PET.
- For suspected LVV, clinical diagnosis without FDG-PET.
- For diverse noncardiac or nononcologic conditions, CT, radiograph, and MRI.

Outcomes
For patients with epilepsy, 2 outcomes of interest are: (1) to identify the epileptic focus accurately before surgery and (2) to predict which patients will have a favorable outcome following surgery.

For patients with suspected AD, suspected chronic osteomyelitis, and suspected LVV, or other noncardiac or nononcologic conditions, outcomes of interest include disease-related morbidity and mortality.

Timing
For patients with epilepsy, FDG-PET would be conducted prior to surgery.

For patients with suspected AD, suspected chronic osteomyelitis, suspected LVV, or other noncardiac or nononcologic conditions, FDG-PET would be performed following inconclusive clinical examinations and standard radiographs.

Setting
FDG-PET is administered in an imaging center equipped with a PET scanner.

Epilepsy
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
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.[19] 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	Outcomes
Jones et al (2016)[22]	1946-2014	27	3163 (25-434)	OBS	Prognostic accuracy
Wang et al (2016)[23]	2000-2015	18	391 (5-86)	NR	Prognostic accuracy
Burneo et al (2015)[24]	1946-2013	39	2650	OBS	Diagnostic/prognostic accuracy, clinical utility
Englot et al (2012)[25]	1990-2010	21[a]	1199 (13-253)[a]	OBS	Prognostic accuracy
Willmann et al (2007)[26]	1992-2006	46	1112 (2-117)	OBS	Prognostic accuracy

FDG-PET: fluorine 18 fluorodeoxyglucose positron emission tomography; OBS: observational.
[a] Total number of studies and participants included; unclear if all studies included PET as a predictor.

Jones et al (2016) published a systematic review of neuroimaging for surgical treatment of temporal lobe epilepsy.[22] 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, MEDLINE, 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 included a search of MEDLINE.[23] Eighteen studies (total 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 vs 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.[24] The literature review included searches of the MEDLINE, 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 (total N=2650 participants) in the qualitative review. Good surgical outcome was defined as Engel class I, II, or III, seizure-free, or significant improvement (<10 seizures per year and at least a 90% reduction in seizures from the preoperative year). Due to heterogeneity in patient populations, study

designs, outcome measurements, and methods of PET interpretation, pooled estimates were not provided; 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 MEDLINE search that had at least 10 participants and 48 months of follow-up.[25] Long-term seizure freedom was defined as Engel class I outcome. Twenty-one studies (total N=1199 patients) were included; the number of studies that specifically addressed PET was not specified. Results are summarized in Table 2. 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 included 46 studies published identified through a MEDLINE search.[26] 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 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 benefit of PET was unclear.

Table 2. Results of Systematic Reviews on Use of FDG-PET for Epilepsy

Study	Studies	N	Outcomes	Estimate or Range	95% CI	I^2	p
Jones et al (2016)[22]	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)[23]	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)[24]	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)[25]	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)[26]	46	1112	Prognostic accuracy (good surgical outcome)	PPV=86%	NR	NR	NR

CI: confidence interval; EEG: electroencephalography; FDG: fluorine 18 fluorodeoxyglucose; 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
In a study published after the most recent systematic reviews, 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).[27] 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.[24] After receiving FDG-PET results on adults, some clinicians changed surgical decisions, used the results to guide intracranial electroencephalography, 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.

Section Summary: 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
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

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.[28] 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 In-oxine 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 (total 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.[29] 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.[30] 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, including 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 (total 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”[31]; (2) 22 trauma patients scheduled for surgery who had suspected metallic implant–associated infection[32]; (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[33]; and (4) 30 consecutive nondiabetic patients referred for possible chronic osteomyelitis.[34] 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.[35] 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 negative predictive value (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 avoid unnecessary 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 (eg, patients with metal hardware).

Section Summary: Suspected Chronic Osteomyelitis
Evidence for the use of FDG-PET to diagnose chronic osteomyelitis includes 3 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 and leukocyte scintigraphy.

Suspected Alzheimer Disease
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 the characteristics and results of several meta-analyses of the early diagnosis of AD in people with cognitive impairment or for differentiating between potential causes of dementia are shown in Tables 3 and 4 and are briefly described below.

Table 3. Characteristics of Systematic Reviews on Use Assessing FDG-PET for AD and Dementia

Study	Dates	Studies	N (Range)	Design	Outcomes
Smailagic et al (2015)[36]	1999-2013	16	697 (19-94)	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Davison et al (2014)[37]	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)[38]	1990-2010	119	NR	OBS	Diagnostic accuracy for diagnosis of AD, differential diagnosis in dementia
Yuan et al (2009)[39]	2001-2005	6	280 (17-128)	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Matchar et al (2001)[40]	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.

Smailagic et al (2015) conducted a Cochrane review to assess the diagnostic accuracy of FDG-PET for detecting people who clinically convert to AD or other forms of dementia at follow-up.[36] Included studies evaluated the diagnostic accuracy of FDG-PET to determine the conversion from mild cognitive impairment (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 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 identified through MEDLINE.[37] 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 3 different studies (271 participants), the sensitivities and specificities of FDG-PET for distinguishing AD from Lewy body dementia ranged from 83% to 99% and from 71% to 93%, respectively. And in 2 studies (183 participants), for predicting conversion from MCI to AD, sensitivity and specificity of PET ranged from 57% to 82% and from 67% to 78%, respectively.

Bloudek et al (2011) assessed diagnostic strategies for AD in a meta-analysis.[38] Reviewers included 119 studies of diagnostic performance characteristics published from 1990 to 2010. Studies were identified through a search of MEDLINE and included imaging, biomarkers, and clinical diagnostic strategies. Twenty studies included performance characteristics of FDG-PET for diagnosing AD compared with normal, nondemented controls. Thirteen studies described characteristics of FDG-PET for diagnosing AD compared with demented controls. FDG-PET demonstrated the highest area under the receiver operating characteristic curve, sensitivity, and specificity among all of the diagnostic methods for distinguishing AD from normal controls but one of the lowest receiver operating characteristic comparing AD with 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, single-photon emission computed tomography, and structural MRI to predict patients' conversion from MCI to AD.[39] 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 (eg, 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 3 clinical populations: patients with dementia, patients with MCI, and subjects with no symptoms but with a first-degree relative with AD.[40] For the review, a search was performed using MEDLINE, 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 that 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)
Smailagic et al (2015)[36]	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)[37]	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)[38]	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)[39]	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)[40]	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.

Retrospective Studies

In a study published after the systematic reviews, Pagani et al (2017) tested the accuracy of FDG-PET to discriminate between patients with MCI who progressed to AD and those who did not progress.[41] The study population consisted of 42 normal elderly patients without MCI, 27 patients with MCI who had not converted to AD after a follow-up of at least 5 years since the first FDG-PET scan (mean follow-up, 7.5 years), and 95 patients with MCI who converted to AD within 5 years of the baseline FDG-PET (mean time to conversion, 1.8 years). The group that progressed to AD within 5 years showed significantly lower FDG-PET uptake values in the temporoparietal cortex than the other groups. Baseline FDG-PET identified patients who converted to AD with an accuracy of 89%.

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.

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 scans were reviewed (N=136).[42] 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. The 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%).

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 poor quality. There is no standard cutoff for positive amyloid findings on PET scanning 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 vs 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

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).

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 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
Lee et al (2016)[43]	Up to 2015	8	400 (21-93)	OBS	Diagnostic accuracy for GCA and TA
Soussan et al (2015)[44]	2000-2013	21	712 (18-93)	OBS	Diagnostic accuracy for GCA; assessment of disease activity in TA
Puppo et al (2014)[45]	1999-2014	19	977 (8-304)	OBS	Diagnostic accuracy for GCA
Treglia et al (2011)[46]	Up to 2011	32	604	OBS	Diagnostic accuracy for GCA and TA; assessment of disease activity; monitor treatment response
Besson et al (2011)[47]	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.

Lee et al (2016) performed a meta-analysis of the diagnostic accuracy of FDG-PET and PET/CT for LVV.[43] The search included studies indexed in PubMed, EMBASE, or Cochrane Library that used the American College of Rheumatology (ACR) classification system as the reference standard diagnosis. Eight studies (total 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 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.[44] The MEDLINE, 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[48] 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 ($p<0.001$). 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 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.[45] Reviewers selected 19 studies (442 cases, 535 controls) found in PubMed or 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 6.

Treglia et al (2011) published a systematic review of PET and PET/CT in patients with LVV.[46] Reviewers searched MEDLINE and Scopus for publications on the role of FDG-PET in LVV. Reviewers identified 32 studies (total 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. They concluded that: (1) PET and PET/CT may be useful for initial diagnosis and assessment of severity of disease; (2) appeared to be superior to MRI in the diagnosis of LVV, but not in assessing disease activity under immunosuppressive treatment, in predicting relapse, or in evaluating vascular complications; (3) the role of these imaging methods in monitoring treatment response is unclear. 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 MEDLINE, EMBASE, and the Cochrane databases.[47] 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 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)
Lee et al (2016)[43]	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)[44]	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)

Study	Studies	N	Outcomes	Estimate (95% CI)
	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)[45]	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)[46]	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)[47]	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.

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.

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 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

Numerous systematic reviews have described the use of PET in patients with carotid stenosis[49]; inflammatory diseases[50,51]; fever of unknown origin[52-54]; hyperinsulinemic hypoglycemia[55,56]; spinal infections[57]; mycobacterium infection[58]; Creutzfeldt-Jakob disease[59]; vascular prosthetic graft infection[60]; prosthetic infection after knee or hip arthroplasty[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.

A systematic review by Treglia et al (2011) addressed the use of FDG-PET in evaluating disease activity in patients with sarcoidosis.[65] It did not include a quality assessment of individual studies. Only 3 small studies of 9 reviewed included data from a comparator imaging modality; thus, conclusions about comparative diagnostic performance cannot be reached.

In a systematic review of FDG-PET to diagnose prosthetic joint infection following hip or knee replacement, Kwee et al (2008) reported on a pooled sensitivity and specificity of 82.1% (95% CI, 68.0% to 90.8%) and 86.6% (95% CI, 79.7% to 91.4%), respectively.[66] Reviewers noted significant heterogeneity among the 11 studies analyzed. Differences in performance were based on the location of prostheses (hip vs knee) and whether filtered back projection or iterative reconstruction was used. This meta-analysis and a study by Reinartz (2009) on the same clinical issue found that the specificity of PET was significantly greater for hip prostheses than for knee prostheses.[67] Both author groups also noted that these results were based on the use of PET alone. CT is generally not useful in evaluating potential infections around joint prostheses because of the artifacts caused by the metallic implants, so additional research would be needed on combined PET/CT. The 2009 study compared the accuracy of PET with a triple-phase scan and with WBC imaging.

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.

Summary of Evidence

For individuals who have epileptic seizures who are candidates for surgery who have 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 Assessments and Program in Evidence-based Care 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 a meaningful improvement in the net health outcome.

For individuals who have suspected chronic osteomyelitis who receive FDG-PET, the evidence includes meta-analyses and a prospective study published after the meta-analyses. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, functional outcomes, quality of life, and hospitalizations. One systematic review and meta-analysis from 2013 of 9 studies revealed that FDG-PET and FDG-PET plus computed tomography were useful for diagnosing suspected osteomyelitis in the foot of patients with diabetes. The results of another meta-analysis (2005) 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 a meaningful improvement in the net health outcome.

For individuals who have suspected Alzheimer disease who receive FDG-PET, the evidence includes 5 systematic reviews of observational studies and a retrospective study assessing clinical utility. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, quality of life, and hospitalizations. The studies included in the reviews were generally of poor quality. There is no standard cutoff for PET positivity for diagnosing Alzheimer disease, and many studies have not included postmortem confirmation of Alzheimer disease as the reference standard, leading to uncertainty about estimates of performance characteristics. FDG-PET may have high sensitivity and specificity for diagnosing Alzheimer disease, but there is little evidence comparing the performance characteristics of clinical diagnosis using PET with the clinical diagnosis not using PET; therefore, the incremental value of adding 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 the effects of the technology on health outcomes.

For individuals who have suspected large vessel vasculitis who receive FDG-PET, the evidence includes 5 systematic reviews of observational studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, morbid events, quality of life, hospitalizations, and treatment-related morbidity. Most studies included in the reviews were small and lacked controls. The reported performance characteristics were heterogeneous, but reviewers were unable to determine the source of heterogeneity. Studies comparing PET with the true reference standard of biopsy or angiography are 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 the effects of the technology on health outcomes.

For individuals who have diverse noncardiac or nononcologic conditions (eg, central nervous system, pulmonary, and musculoskeletal diseases) who receive FDG-PET, the evidence includes a few systematic reviews. Relevant outcomes are overall survival, symptoms, change in disease

status, functional outcomes, health status measures, quality of life, hospitalizations, medication use, and resource utilization. Many studies cited in the reviews were small, retrospective, and published in the 1990s to early 2000s; 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 FDG-PET results can change management, and therefore improve patient outcomes to support the utility of FDG-PET. The evidence is insufficient to determine the effect of the technology on health outcomes

Practice Guidelines and Position Statements

American Academy of Neurology

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

Table 7. Practice Parameters on Diagnosis of Dementia

Practice Parameter	Date	PET Recommendation
Diagnosis of dementia[68]	2004: reaffirmed	PET imaging not recommended for routine use in diagnostic evaluation of dementia (LOR: moderate clinical certainty)
Early detection of dementia[69]	2003: reaffirmed	Not addressed
Diagnosis of new-onset PD[70]	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[71]	2006; retired 2018	Not addressed
Mild cognitive impairment[72]	2001; 2017	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 (2010) published evidence-based, consensus guidelines.[73] Fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) was considered:

> "an option in patients in whom diagnosis of periprosthetic joint infection has not been established and are not scheduled for reoperation. (Strength of recommendation: limited [quality of the supporting evidence is unconvincing, or well-conducted studies show little clear advantage of one approach over another])"

American College of Radiology

Evidence- and consensus-based appropriateness criteria from 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)[74]	2017	• Usually not appropriate for: (1) suspected osteomyelitis with soft tissue or juxta-articular swelling with cellulitis and a skin lesion, injury, wound, ulcer, or blister; or (2) suspected osteomyelitis with pain and swelling or cellulitis associated with site of previous nonarthroplasty hardware. • Usually not appropriate for suspected osteomyelitis with soft-tissue or juxta-articular swelling with a history of surgery, though "this is promising new technology but data are limited."
Diagnosis of dementia[75]	2001, reaffirmed 2004	PET imaging not recommended for routine use in diagnostic evaluation of dementia (LOR: moderate clinical certainty)
Early detection of dementia[75]	2001, reaffirmed 2003, 2015	Not addressed
Diagnosis of new onset-PD[75]	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[75]	2006	Not addressed
Dementia and movement disorders[76]	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[77]	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[78]	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[79]	2014	Usually not appropriate
Fever without source – child[80]	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[81]	2012	Usually not appropriate

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; PD: Parkinson disease; PET: positron emission tomography.

Infectious Diseases Society of America

The Infectious Diseases Society of America (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."

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]).

IDSA (2012) published evidence-based, consensus guidelines on the diagnosis and treatment of diabetic foot infections.[84] The guidelines concluded that the role of FDG-PET in evaluating a diabetic foot infection has not been established.

IDSA (2018) will be publishing guidelines on the diagnosis and management of bone and joint infections in children.

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 2018 (ongoing)
NCT03022968	Tau Brain Imaging in Typical and Atypical Alzheimer's Disease	24	Sep 2018
NCT02084147	PET-MRI: Evaluation, Optimization and Clinical Implementation	530	Oct 2018
NCT00194298	FDG-PET Imaging in Complicated Diabetic Foot	240	Jan 2020
NCT02771483	Improving the Diagnosis and Prognostication of Giant Cell Arteritis through the Novel Use of Positron Emission Tomography (PET), Microbiological and Immune Biomarkers	50	Feb 2020
Unpublished			
NCT00329706	Early and Long-Term Value of Imaging Brain Metabolism	710	Jan 2017 (completed)

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.

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 (eg, 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 (eg, 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

- A PET scan essentially involves 3 separate activities:
  1) manufacture of the radiopharmaceutical, which may be manufactured on site, or at a regional delivery center with delivery to the institution performing PET;
  2) actual performance of the PET scan; and
  3) interpretation of the results.

ICD-10 Diagnoses (Effective October 1, 2015)

G40.011	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, with status epilepticus
G40.019	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, without status epilepticus
G40.111	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, with status epilepticus
G40.119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, without status epilepticus
G40.211	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, with status epilepticus
G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, without status epilepticus
M86.311	Chronic multifocal osteomyelitis, right shoulder
M86.312	Chronic multifocal osteomyelitis, left shoulder
M86.321	Chronic multifocal osteomyelitis, right humerus
M86.322	Chronic multifocal osteomyelitis, left humerus
M86.331	Chronic multifocal osteomyelitis, right radius and ulna

M86.332 Chronic multifocal osteomyelitis, left radius and ulna
M86.341 Chronic multifocal osteomyelitis, right hand
M86.342 Chronic multifocal osteomyelitis, left hand
M86.351 Chronic multifocal osteomyelitis, right femur
M86.352 Chronic multifocal osteomyelitis, left femur
M86.361 Chronic multifocal osteomyelitis, right tibia and fibula
M86.362 Chronic multifocal osteomyelitis, left tibia and fibula
M86.371 Chronic multifocal osteomyelitis, right ankle and foot
M86.372 Chronic multifocal osteomyelitis, left ankle and foot
M86.38 Chronic multifocal osteomyelitis, other site
M86.39 Chronic multifocal osteomyelitis, multiple sites
M86.411 Chronic osteomyelitis with draining sinus, right shoulder
M86.412 Chronic osteomyelitis with draining sinus, left shoulder
M86.421 Chronic osteomyelitis with draining sinus, right humerus
M86.422 Chronic osteomyelitis with draining sinus, left humerus
M86.431 Chronic osteomyelitis with draining sinus, right radius and ulna
M86.432 Chronic osteomyelitis with draining sinus, left radius and ulna
M86.441 Chronic osteomyelitis with draining sinus, right hand
M86.442 Chronic osteomyelitis with draining sinus, left hand
M86.451 Chronic osteomyelitis with draining sinus, right femur
M86.452 Chronic osteomyelitis with draining sinus, left femur
M86.461 Chronic osteomyelitis with draining sinus, right tibia and fibula
M86.462 Chronic osteomyelitis with draining sinus, left tibia and fibula
M86.471 Chronic osteomyelitis with draining sinus, right ankle and foot
M86.472 Chronic osteomyelitis with draining sinus, left ankle and foot
M86.48 Chronic osteomyelitis with draining sinus, other site
M86.49 Chronic osteomyelitis with draining sinus, multiple sites
M86.511 Other chronic hematogenous osteomyelitis, right shoulder
M86.512 Other chronic hematogenous osteomyelitis, left shoulder
M86.521 Other chronic hematogenous osteomyelitis, right humerus
M86.522 Other chronic hematogenous osteomyelitis, left humerus
M86.531 Other chronic hematogenous osteomyelitis, right radius and ulna
M86.532 Other chronic hematogenous osteomyelitis, left radius and ulna
M86.541 Other chronic hematogenous osteomyelitis, right hand
M86.542 Other chronic hematogenous osteomyelitis, left hand
M86.551 Other chronic hematogenous osteomyelitis, right femur
M86.552 Other chronic hematogenous osteomyelitis, left femur
M86.561 Other chronic hematogenous osteomyelitis, right tibia and fibula
M86.562 Other chronic hematogenous osteomyelitis, left tibia and fibula
M86.571 Other chronic hematogenous osteomyelitis, right ankle and foot
M86.572 Other chronic hematogenous osteomyelitis, left ankle and foot
M86.58 Other chronic hematogenous osteomyelitis, other site
M86.59 Other chronic hematogenous osteomyelitis, multiple sites
M86.60 Other chronic osteomyelitis, unspecified site
M86.611 Other chronic osteomyelitis, right shoulder
M86.612 Other chronic osteomyelitis, left shoulder
M86.621 Other chronic osteomyelitis, right humerus
M86.622 Other chronic osteomyelitis, left humerus

M86.631 Other chronic osteomyelitis, right radius and ulna
M86.632 Other chronic osteomyelitis, left radius and ulna
M86.641 Other chronic osteomyelitis, right hand
M86.642 Other chronic osteomyelitis, left hand
M86.651 Other chronic osteomyelitis, right thigh
M86.652 Other chronic osteomyelitis, left thigh
M86.661 Other chronic osteomyelitis, right tibia and fibula
M86.662 Other chronic osteomyelitis, left tibia and fibula
M86.671 Other chronic osteomyelitis, right ankle and foot
M86.672 Other chronic osteomyelitis, left ankle and foot
M86.68 Other chronic osteomyelitis, other site
M86.69 Other chronic osteomyelitis, multiple sites

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: " 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

REVISONS	
	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 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 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.

REVISONS	
	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" ▪ 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

REFERENCES

1. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med.* Sep 8 2011;365(10):919-926. PMID 21899452
2. Mishra AM, Bai H, Gribizis A, et al. Neuroimaging biomarkers of epileptogenesis. *Neurosci Lett.* Jun 27 2011;497(3):194-204. PMID 21303682
3. Engel J, Cascino G, Ness P, et al. Outcome with respect to epileptic seizures. In: Engel J, ed. *Surgical Treatment of the Epilepsies*. New York, NY: Raven Press; 1993:609-621.

4. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis.* Oct 1 2004;39(7):885-910. PMID 15472838
5. Dinh MT, Abad CL, Safdar N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. *Clin Infect Dis.* Aug 15 2008;47(4):519-527. PMID 18611152
6. Beckett LA, Harvey DJ, Gamst A, et al. The Alzheimer's Disease Neuroimaging Initiative: annual change in biomarkers and clinical outcomes. *Alzheimers Dement.* May 2010;6(3):257-264. PMID 20451874
7. Mosconi L, Tsui WH, Herholz K, et al. Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. *J Nucl Med.* Mar 2008;49(3):390-398. PMID 18287270
8. Szelies B, Mielke R, Herholz K, et al. Quantitative topographical EEG compared to FDG PET for classification of vascular and degenerative dementia. *Electroencephalogr Clin Neurophysiol.* Aug 1994;91(2):131-139. PMID 7519142
9. Dolan RJ, Bench CJ, Brown RG, et al. Regional cerebral blood flow abnormalities in depressed patients with cognitive impairment. *J Neurol Neurosurg Psychiatry.* Sep 1992;55(9):768-773. PMID 1402966
10. Gulati A, Bagga A. Large vessel vasculitis. *Pediatr Nephrol.* Jun 2010;25(6):1037-1048. PMID 19844748
11. Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum.* Aug 1990;33(8):1129-1134. PMID 1975175
12. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* Aug 1990;33(8):1122-1128. PMID 2202311
13. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* Jan 2013;65(1):1-11. PMID 23045170
14. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis.* Mar 2009;68(3):318-323. PMID 18413441
15. Food and Drug Administration (FDA). PET Drugs - Current Good Manufacturing Practice (CGMP). 2009; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070306.pdf. Accessed August 24, 2018.
16. Food and Drug Administration (FDA). PET Drugs - Current Good Manufacturing Practice (CGMP) Small Entity Compliance Guide. 2011; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM266640.pdf. Accessed August 24, 2018.
17. Food and Drug Administration (FDA). Guidance: Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs. 2012; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291573.pdf. Accessed August 24, 2018.
18. Food and Drug Administration (FDA). Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications. *Federal Register.* 2000;65(48):12999-13010.
19. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) in the Management of Seizure Disorders. *TEC Assessments.* 1996;Volume 11:Tab 33.
20. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) for the Assessment of Cerebrovascular Disease. *TEC Assessments.* 1996;Volume 11:Tab 35.
21. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Positron Emission Tomography (PET) of Central Nervous System Diseases. *TEC Assessments.* 1992;Volume 7:Tab 3.
22. Jones AL, Cascino GD. Evidence on use of neuroimaging for surgical treatment of temporal lobe epilepsy: a systematic review. *JAMA Neurol.* Apr 1 2016;73(4):464-470. PMID 26926529

23. Wang X, Zhang C, Wang Y, et al. Prognostic factors for seizure outcome in patients with MRI-negative temporal lobe epilepsy: A meta-analysis and systematic review. *Seizure.* May 2016;38:54-62. PMID 27182689
24. Burneo JG, Poon R, Kellett S, et al. The utility of positron emission tomography in epilepsy. *Can J Neurol Sci.* Nov 2015;42(6):360-371. PMID 26437611
25. Englot DJ, Wang DD, Rolston JD, et al. Rates and predictors of long-term seizure freedom after frontal lobe epilepsy surgery: a systematic review and meta-analysis. *J Neurosurg.* May 2012;116(5):1042-1048. PMID 22304450
26. Willmann O, Wennberg R, May T, et al. The contribution of 18F-FDG PET in preoperative epilepsy surgery evaluation for patients with temporal lobe epilepsy A meta-analysis. *Seizure.* Sep 2007;16(6):509-520. PMID 17532231
27. Traub-Weidinger T, Weidinger P, Groppel G, et al. Presurgical evaluation of pediatric epilepsy patients prior to hemispherotomy: the prognostic value of 18F-FDG PET. *J Neurosurg Pediatr.* Dec 2016;25(6):683-688. PMID 27611898
28. Lauri C, Tamminga M, Glaudemans A, et al. Detection of osteomyelitis in the diabetic foot by imaging techniques: a systematic review and meta-analysis comparing MRI, white blood cell scintigraphy, and FDG-PET. *Diabetes Care.* Aug 2017;40(8):1111-1120. PMID 28733376
29. Treglia G, Sadeghi R, Annunziata S, et al. Diagnostic performance of Fluorine-18-Fluorodeoxyglucose positron emission tomography for the diagnosis of osteomyelitis related to diabetic foot: a systematic review and a meta-analysis. *Foot (Edinb).* Dec 2013;23(4):140-148. PMID 23906976
30. Termaat MF, Raijmakers PG, Scholten HJ, et al. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. *J Bone Joint Surg Am.* Nov 2005;87(11):2464-2471. PMID 16264122
31. de Winter F, van de Wiele C, Vogelaers D, et al. Fluorine-18 fluorodeoxyglucose-position emission tomography: a highly accurate imaging modality for the diagnosis of chronic musculoskeletal infections. *J Bone Joint Surg Am.* May 2001;83-A(5):651-660. PMID 11379733
32. Schiesser M, Stumpe KD, Trentz O, et al. Detection of metallic implant-associated infections with FDG PET in patients with trauma: correlation with microbiologic results. *Radiology.* Feb 2003;226(2):391-398. PMID 12563131
33. Guhlmann A, Brecht-Krauss D, Suger G, et al. Fluorine-18-FDG PET and technetium-99m antigranulocyte antibody scintigraphy in chronic osteomyelitis. *J Nucl Med.* Dec 1998;39(12):2145-2152. PMID 9867159
34. Meller J, Koster G, Liersch T, et al. Chronic bacterial osteomyelitis: prospective comparison of (18)F-FDG imaging with a dual-head coincidence camera and (111)In-labelled autologous leucocyte scintigraphy. *Eur J Nucl Med Mol Imaging.* Jan 2002;29(1):53-60. PMID 11807607
35. Rastogi A, Bhattacharya A, Prakash M, et al. Utility of PET/CT with fluorine-18-fluorodeoxyglucose-labeled autologous leukocytes for diagnosing diabetic foot osteomyelitis in patients with Charcot's neuroarthropathy. *Nucl Med Commun.* Dec 2016;37(12):1253-1259. PMID 27749777
36. Smailagic N, Vacante M, Hyde C, et al. (1)(8)F-FDG PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* Jan 28 2015;1:CD010632. PMID 25629415
37. Davison CM, O'Brien JT. A comparison of FDG-PET and blood flow SPECT in the diagnosis of neurodegenerative dementias: a systematic review. *Int J Geriatr Psychiatry.* Jun 2014;29(6):551-561. PMID 24123413
38. Bloudek LM, Spackman DE, Blankenburg M, et al. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. *J Alzheimers Dis.* Jun 2011;26(4):627-645. PMID 21694448
39. Yuan Y, Gu ZX, Wei WS. Fluorodeoxyglucose-positron-emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to Alzheimer disease in patients with mild cognitive impairment: a meta-analysis. *AJNR Am J Neuroradiol.* Feb 2009;30(2):404-410. PMID 19001534

40. Matchar DB, Kulasingam SL, McCrory DC, et al. *Use of Positron Emission Tomography and Other Neuroimaging Techniques in the Diagnosis and Management of Alzheimer's Disease and Dementia.* Rockville, MD: Agency for Healthcare Research and Quality; 2001.
41. Pagani M, Nobili F, Morbelli S, et al. Early identification of MCI converting to AD: a FDG PET study. *Eur J Nucl Med Mol Imaging.* Nov 2017;44(12):2042-2052. PMID 28664464
42. Motara H, Olusoga T, Russell G, et al. Clinical impact and diagnostic accuracy of 2-[18F]-fluoro-2-deoxy-d-glucose positron-emission tomography/computed tomography (PET/CT) brain imaging in patients with cognitive impairment: a tertiary centre experience in the UK. *Clin Radiol.* Jan 2017;72(1):63-73. PMID 27637430
43. Lee YH, Choi SJ, Ji JD, et al. Diagnostic accuracy of 18F-FDG PET or PET/CT for large vessel vasculitis : A meta-analysis. *Z Rheumatol.* Nov 2016;75(9):924-931. PMID 26704559
44. Soussan M, Nicolas P, Schramm C, et al. Management of large-vessel vasculitis with FDG-PET: a systematic literature review and meta-analysis. *Medicine (Baltimore).* Apr 2015;94(14):e622. PMID 25860208
45. Puppo C, Massollo M, Paparo F, et al. Giant cell arteritis: a systematic review of the qualitative and semiquantitative methods to assess vasculitis with 18F-fluorodeoxyglucose positron emission tomography. *Biomed Res Int.* Sep 2014;2014:574248. PMID 25254211
46. Treglia G, Mattoli MV, Leccisotti L, et al. Usefulness of whole-body fluorine-18-fluorodeoxyglucose positron emission tomography in patients with large-vessel vasculitis: a systematic review. *Clin Rheumatol.* Oct 2011;30(10):1265-1275. PMID 21833685
47. Besson FL, Parienti JJ, Bienvenu B, et al. Diagnostic performance of (1)(8)F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* Sep 2011;38(9):1764-1772. PMID 21559981
48. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. *Ann Intern Med.* Jun 1 1994;120(11):919-929. PMID 7909656
49. Gupta A, Baradaran H, Schweitzer AD, et al. Oxygen extraction fraction and stroke risk in patients with carotid stenosis or occlusion: a systematic review and meta-analysis. *AJNR Am J Neuroradiol.* Feb 2014;35(2):250-255. PMID 23945227
50. Yan J, Zhang C, Niu Y, et al. The role of 18F-FDG PET/CT in infectious endocarditis: a systematic review and meta-analysis. *Int J Clin Pharmacol Ther.* May 2016;54(5):337-342. PMID 27008000
51. Mackie SL, Koduri G, Hill CL, et al. Accuracy of musculoskeletal imaging for the diagnosis of polymyalgia rheumatica: systematic review. *RMD Open.* Nov 2015;1(1):e000100. PMID 26535139
52. Hao R, Yuan L, Kan Y, et al. Diagnostic performance of 18F-FDG PET/CT in patients with fever of unknown origin: a meta-analysis. *Nucl Med Commun.* Jul 2013;34(7):682-688. PMID 23636293
53. Besson FL, Chaumet-Riffaud P, Playe M, et al. Contribution of (18)F-FDG PET in the diagnostic assessment of fever of unknown origin (FUO): a stratification-based meta-analysis. *Eur J Nucl Med Mol Imaging.* Sep 2016;43(10):1887-1895. PMID 27037917
54. Bharucha T, Rutherford A, Skeoch S, et al. Diagnostic yield of FDG-PET/CT in fever of unknown origin: a systematic review, meta-analysis, and Delphi exercise. *Clin Radiol.* Sep 2017;72(9):764-771. PMID 28600002
55. Kapoor RR, James C, Hussain K. Advances in the diagnosis and management of hyperinsulinemic hypoglycemia. *Nat Clin Pract Endocrinol Metab.* Feb 2009;5(2):101-112. PMID 19165222
56. Yang J, Hao R, Zhu X. Diagnostic role of 18F-dihydroxyphenylalanine positron emission tomography in patients with congenital hyperinsulinism: a meta-analysis. *Nucl Med Commun.* Apr 2013;34(4):347-353. PMID 23376859
57. Prodromou ML, Ziakas PD, Poulou LS, et al. FDG PET is a robust tool for the diagnosis of spondylodiscitis: a meta-analysis of diagnostic data. *Clin Nucl Med.* Apr 2014;39(4):330-335. PMID 24445277
58. Treglia G, Taralli S, Calcagni ML, et al. Is there a role for fluorine 18 fluorodeoxyglucose-positron emission tomography and positron emission tomography/computed tomography in evaluating patients with mycobacteriosis? A systematic review. *J Comput Assist Tomogr.* May-Jun 2011;35(3):387-393. PMID 21586936

59. Caobelli F, Cobelli M, Pizzocaro C, et al. The role of neuroimaging in evaluating patients affected by Creutzfeldt-Jakob disease: a systematic review of the literature. *J Neuroimaging.* Jan 2015;25(1):2-13. PMID 24593302
60. Saleem BR, Pol RA, Slart RH, et al. 18F-Fluorodeoxyglucose positron emission tomography/CT scanning in diagnosing vascular prosthetic graft infection. *Biomed Res Int.* Sep 2014;2014:471971. PMID 25210712
61. Jin H, Yuan L, Li C, et al. Diagnostic performance of FDG PET or PET/CT in prosthetic infection after arthroplasty: a meta-analysis. *Q J Nucl Med Mol Imaging.* Mar 2014;58(1):85-93. PMID 24469570
62. Zhang J, Li LF, Zhu YJ, et al. Diagnostic performance of 18F-FDG-PET versus scintigraphy in patients with inflammatory bowel disease: a meta-analysis of prospective literature. *Nucl Med Commun.* Dec 2014;35(12):1233-1246. PMID 25192191
63. Niccolini F, Politis M. A systematic review of lessons learned from PET molecular imaging research in atypical parkinsonism. *Eur J Nucl Med Mol Imaging.* Nov 2016;43(12):2244-2254. PMID 27470326
64. Pagano G, Niccolini F, Politis M. Current status of PET imaging in Huntington's disease. *Eur J Nucl Med Mol Imaging.* Jun 2016;43(6):1171-1182. PMID 26899245
65. Treglia G, Taralli S, Giordano A. Emerging role of whole-body 18F-fluorodeoxyglucose positron emission tomography as a marker of disease activity in patients with sarcoidosis: a systematic review. *Sarcoidosis Vasc Diffuse Lung Dis.* Oct 2011;28(2):87-94. PMID 22117499
66. Kwee TC, Kwee RM, Alavi A. FDG-PET for diagnosing prosthetic joint infection: systematic review and metaanalysis. *Eur J Nucl Med Mol Imaging.* Nov 2008;35(11):2122-2132. PMID 18704405
67. Reinartz P. FDG-PET in patients with painful hip and knee arthroplasty: technical breakthrough or just more of the same. *Q J Nucl Med Mol Imaging.* Feb 2009;53(1):41-50. PMID 19182727
68. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* May 8 2001;56(9):1143-1153. PMID 11342678
69. Petersen RC, Stevens JC, Ganguli M, et al. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* May 8 2001;56(9):1133-1142. PMID 11342677
70. Suchowersky O, Reich S, Perlmutter J, et al. Practice Parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* Apr 11 2006;66(7):968-975. PMID 16606907
71. Aarsland D, Emre M, Lees A, et al. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* Jan 2 2007;68(1):80; author reply 81. PMID 17200503
72. American Academy of Neurology. Guideline Summary: Practice guideline update summary: mild cognitive impairment: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. 2018; https://www.guidelinecentral.com/summaries/practice-guideline-update-summary-mild-cognitive-impairment-report-of-the-guideline-development-dissemination-and-implementation-subcommittee-of-the-american-academy-of-neurology/#section-405. Accessed August 24, 2018.
73. American Academy of Orthopaedic Surgeons (AAOS). The diagnosis of periprosthetic joint infections of the hip and knee: guideline and evidence report. 2010; https://www.aaos.org/research/guidelines/PJIguideline.pdf. Accessed August 24, 2018.
74. Expert Panel on Musculoskeletal Imaging, Beaman FD, von Herrmann PF, et al. ACR Appropriateness Criteria(R) suspected osteomyelitis, septic arthritis, or soft tissue infection (excluding spine and diabetic foot). *J Am Coll Radiol.* May 2017;14(5S):S326-S337. PMID 28473089
75. American College of Radiology (ACR). ACR appropriateness criteria: dementia and movement disorders. 2015; https://acsearch.acr.org/list. Accessed August 24, 2018.
76. Frey KA, Lodge MA, Meltzer CC, et al. ACR-ASNR practice parameter for brain PET/CT imaging dementia. *Clin Nucl Med.* Feb 2016;41(2):118-125. PMID 26646994
77. American College of Radiology (ACR). ACR appropriateness criteria: imaging after total knee arthroplasty. 2017; https://acsearch.acr.org/list. Accessed August 24, 2018.

78. American College of Radiology (ACR). ACR appropriateness criteria: seizures and epilepsy. 2014; https://acsearch.acr.org/list. Accessed August 24, 2018.
79. American College of Radiology (ACR). ACR appropriateness criteria: Crohn disease. 2014; https://acsearch.acr.org/list. Accessed August 24, 2018.
80. American College of Radiology (ACR). ACR appropriateness criteria: fever without source or unknown origin--child. 2015; https://acsearch.acr.org/list. Accessed August 24, 2018.
81. American College of Radiology (ACR). ACR appropriateness criteria: suspected osteomyelitis of the foot in patients with diabetes mellituse: 2012. 2012; https://acsearch.acr.org/list. Accessed August 24, 2018.
82. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis.* Sep 15 2015;61(6):e26-46. PMID 26229122
83. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* Jan 2013;56(1):e1-e25. PMID 23223583
84. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis.* Jun 2012;54(12):e132-173. PMID 22619242
85. Centers for Medicare & Medicaid Services (CMS). Decision Memo for Positron Emission Tomography (FDG) and Other Neuroimaging Devices for Suspected Dementia (CAG-00088R). 2004; https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=104&NcaName=Positron+Emission+Tomography+(FDG)+and+Other+Neuroimaging+Devices+for+Suspected+Dementia+(1st+Recon)&bc=AiAAAAAAEAAA&. Accessed August 24, 2018.
86. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for FDG PET for Dementia and Neurodegenerative Diseases (220.6.13). 2009; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=288&ncdver=3&DocID=220.6.13&SearchType=Advanced&bc=IAAAABAAAAAAAA%3d%3d&. Accessed August 24, 2018.
87. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination for FDG PET for Infection and Inflammation (220.6.16). 2008; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=323&ncdver=1&CoverageSelection=National&KeyWord=pet&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAABAAAAAAAA%3d%3d&. Accessed August 24, 2018.

Other References

1. Blue Cross and Blue Shield of Kansas, Medical Advisory Committee meeting, April 24, 2003 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report MAC–02-03).
2. Blue Cross and Blue Shield of Kansas, Oncology Liaison Committee meeting, February 18, 2003 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report MAC–02-03).
3. Blue Cross and Blue Shield of Kansas, Radiology Liaison Committee meeting, February 11, 2003 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report MAC–02-03).
4. MCMC, Medical Care Ombudsman Program (MCOP), August 11, 2006, MCOP ID 1071-0720.
5. Considine oncology consultant (#372), January 23, 2007, Reference: Semin Nucl Med. 2006 Jan;36(1):93-104. Links Positron emission tomography in gynecologic cancer. Yen TC, Lai CH.
6. Blue Cross and Blue Shield of Kansas Radiology Liaison Committee, February 2009.