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Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography

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Related Policies
6.01.20 Cardiac Applications of Positron Emission Tomography Scanning
6.01.26 Oncologic Applications of Positron Emission Tomography Scanning
6.01.51 Interim Positron Emission Tomography Scanning in Oncology to Detect Early Response During Treatment
6.01.55 β-Amyloid Imaging With Positron Emission Tomography for Alzheimer Disease

Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography

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
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	• 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	• Test accuracy • Test validity • Other test performance measures • Symptoms • Morbid events • Quality of life • Hospitalizations • Treatment-related morbidity
Individuals:	Interventions of	Comparators of interest are:	Relevant outcomes include:

• With diverse noncardiac or nononcologic conditions (eg, central nervous system, pulmonary, and musculoskeletal diseases)	interest are: • Fluorine 18 fluorodeoxyglucose positron emission tomography	• Computed tomography • Plain radiograph • Magnetic resonance imaging	• Overall survival • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life • Hospitalizations • Medication use • Resource utilization

SUMMARY

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

For individuals who have epileptic seizures who are candidates for surgery who have fluorine 18 fluorodeoxyglucose PET (FDG-PET), the evidence includes 5 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 both 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 2 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 the second meta-analysis from 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 addressing 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 connect the PET results in individual patients to improved clinical outcomes. Additional studies are needed to demonstrate FDG-PET results can change management, and therefore improve patient outcomes to determine that FDG-PET is a clinically useful test. The evidence is insufficient to determine the effect of the technology on health outcomes.

OBJECTIVE

The objective of this evidence review is to evaluate the technical reliability, and clinical validity/utility, and clinical utility of fluorine 18 fluorodeoxyglucose positron emission tomography on the net health outcome in individuals with epilepsy, suspected chronic osteomyelitis, suspected Alzheimer disease, suspected large- vessel vasculitis, and other noncardiac and nononcologic conditions.

POLICY

Positron emission tomography (PET) using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) may be considered **medically necessary** in:

1. the assessment of select patients with epileptic seizures who are candidates for surgery (see Policy Guidelines section)
2. the diagnosis of chronic osteomyelitis.

The use of FDG-PET for all other miscellaneous indications is **investigational**, including, but not limited to:

Central Nervous System Diseases

- Autoimmune disorders with central nervous system manifestations, including:
  - Behçet syndrome
  - lupus erythematosus
- Cerebrovascular diseases, including:
  - arterial occlusive disease (arteriosclerosis, atherosclerosis)
  - carotid artery disease
  - cerebral aneurysm
  - cerebrovascular malformations (arteriovenous malformation and Moya-Moya disease)
  - hemorrhage
  - infarct
  - ischemia
- Degenerative motor neuron diseases, including:
  - amyotrophic lateral sclerosis
  - Friedreich ataxia
  - olivopontocerebellar atrophy
  - Parkinson disease
  - progressive supranuclear palsy
  - Shy-Drager syndrome
  - spinocerebellar degeneration

  - Steele-Richardson-Olszewski syndrome
  - Tourette syndrome
- Dementias, including:
  - Alzheimer disease
  - multi-infarct dementia
  - Pick disease
  - frontotemporal dementia
  - dementia with Lewy bodies
  - presenile dementia
- Demyelinating diseases, such as multiple sclerosis
- Developmental, congenital, or inherited disorders, including:
  - adrenoleukodystrophy
  - Down syndrome
  - Huntington chorea
  - kinky-hair disease (Menkes disease)
  - Sturge-Weber syndrome (encephalofacial angiomatosis) and the phakomatoses
- Miscellaneous
  - chronic fatigue syndrome
  - sick building syndrome
  - posttraumatic stress disorder
- Nutritional or metabolic diseases and disorders, including:
  - acanthocytosis
  - hepatic encephalopathy
  - hepatolenticular degeneration
  - metachromatic leukodystrophy
  - mitochondrial disease
  - subacute necrotizing encephalomyelopathy
- Psychiatric diseases and disorders, including:
  - affective disorders
  - depression
  - obsessive-compulsive disorder
  - psychomotor disorders
  - schizophrenia
- Pyogenic infections, including:
  - aspergillosis
  - encephalitis
- Substance abuse, including the central nervous system effects of alcohol, cocaine, and heroin
- Trauma, including brain injury and carbon monoxide poisoning
- Viral infections, including:
  - HIV/AIDS
  - AIDS dementia complex
  - Creutzfeldt-Jakob syndrome
  - progressive multifocal leukoencephalopathy
  - progressive rubella encephalopathy
  - subacute sclerosing panencephalitis
- Mycobacterium infection
- Migraine
- Anorexia nervosa
- Assessment of cerebral blood flow in newborns
  - Vegetative vs locked-in syndrome

Pulmonary Diseases

- Adult respiratory distress syndrome

- Diffuse panbronchiolitis
- Emphysema
- Obstructive lung disease
- Pneumonia

Musculoskeletal Diseases

- Spondylodiscitis
- Joint replacement follow-up

Other

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

POLICY GUIDELINES

In patients with epileptic seizures, appropriate candidates are patients with complex partial seizures who have failed to respond to medical therapy and have been advised to have a resection of a suspected epileptogenic focus located in a region of the brain accessible to surgery. Further, for the purposes of this review, conventional noninvasive techniques for seizure localization must have been tried with results suggesting a seizure focus but not sufficiently conclusive to permit surgery. The purpose of the positron emission tomography (PET) examination should be to avoid subjecting the 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.

CODING

A PET scan 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. The following CPT codes may be used.

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) imaging with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; limited area (eg, chest, head/neck)
78815: Positron emission tomography (PET) imaging with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; skull base to mid-thigh
78816: Positron emission tomography (PET) imaging with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; whole body

There is a HCPCS code specific to the fluorodeoxyglucose (FDG) radiotracer:

A9552: Fluorodeoxyglucose F-18 FDG, diagnostic, per study dose, up to 45 millicuries

BENEFIT APPLICATION

BLUECARD/NATIONAL ACCOUNT ISSUES

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

BACKGROUND

POSITRON EMISSION TOMOGRAPHY

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

A variety of tracers are used for PET scanning, including oxygen 15, nitrogen 13, carbon 11, and fluorine 18. 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 epilepsy surgery. Many effective surgical procedures are available and the treatment selected depends on characteristics of the seizures (eg, the epileptogenic zone) and the extent to which it can be resected safely. Neuroimaging techniques, such as magnetic resonance imaging (MRI), electroencephalography (EEG), PET, single-photon emission computed tomography (SPECT), electric 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 evidence review only addresses the use of radiotracers detected with the use of dedicated full-ring PET scanners. Radiotracers such as FDG may be detected using SPECT cameras, a hybrid PET/SPECT procedure that may be referred to as FDG-SPECT or molecular coincidence detection. The use of SPECT cameras for PET radiotracers presents unique issues of diagnostic performance and is not considered herein.

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….". (Note that many manufacturers have NDAs for FDG.)[18]

Multiple manufacturers have approved NDAs for FDG.

See related evidence reviews 6.01.26 and 6.01.51 for oncologic indications and 6.01.20 for cardiac indications for FDG.

RATIONALE

This evidence review was created in December 1995 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through July 25, 2017. The review was informed in part by on 3 TEC Assessments that addressed various applications of positron emission tomography (PET).[19-21]

Assessment of diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, positive [PPV] and negative predictive values [NPV]) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes).

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, 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 Alzheimer disease, suspected LVV, or other noncardiac or nononcologic conditions?

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

Patients

The population of interest includes patients with epilepsy, chronic osteomyelitis, suspected Alzheimer disease, suspected LVV, or other noncardiac or nononcologic conditions.

Interventions

The intervention of interest is FDG-PET.

Comparators

The comparators of interest for each of the indications include:

- For epilepsy, ictal scalp electroencephalography and magnetic resonance imaging (MRI).
- For suspected chronic osteomyelitis, computed tomography (CT), radiograph, technetium 99 bone scintigraphy, leukocyte scintigraphy, and MRI.
- For suspected Alzheimer disease, 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 Alzheimer disease, suspected chronic osteomyelitis, and suspected LVV, or other noncardiac or nononcologic conditions, the outcome of interest is a confirmed diagnoses. With confirmed diagnoses, appropriate treatment options can be pursued.

Timing

For patients with epilepsy, FDG-PET would be conducted prior to surgery. For patients with suspected Alzheimer disease, suspected chronic osteomyelitis, suspected LVV or other noncardiac or nononcologic conditions, FDG-PET would be performed following clinical examinations and standard radiographs that are inconclusive.

Setting
The setting is an imaging center equipped with a PET scanner.

Epilepsy

Clinical Validity

Systematic Reviews
A 1996 TEC Assessment reviewed evidence on the use of PET in individuals with seizure disorders from 12 studies in which the results of PET scans were correlated with results of an appropriate reference standard test.[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%. The TEC Assessment concluded that because localization can be improved with PET, selection of surgical candidates is improved and, therefore, PET for assessing patients who have medically refractory complex partial seizures and are potential candidates for surgery met TEC criteria. All other uses of PET for the management of seizure disorders did not meet the TEC criteria. Summaries of characteristics and results of several meta-analyses of FDG-PET published since the 1996 TEC Assessment that have assessed either presurgical planning of patients who are candidates for epilepsy surgery or prediction of surgical outcomes are shown in Tables 1 and 2 and are briefly described below.

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

Study (Year)	Dates	No. of Studies	N (Range)	Study Design	Outcome
Jones et al (2016)[22]	1988-2014	11	1358 (21-484)	OBS	Prognostic accuracy
Wang et al (2016)[23]	2000-2015	18	391 (5-86)	NR	Prognostic accuracy
Burneo et al (2015)[24]	1946-2013	5	NR	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; NR: not reported; OBS: observational.
[a] Total number of studies and participants included; unclear if all studies included positron emission tomography as a predictor.

Jones et al published a systematic review of neuroimaging for surgical treatment of temporal lobe epilepsy in 2016.[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 from 1988 to 2014. Twenty-seven studies with 3163 patients were included in the review and 11 of these studies with 1358 patients (all observational designs) evaluated FDG-PET. Good surgical outcome was defined as Engel classes I and II. Meta-analysis was not performed. Results are summarized in Table 2.

A 2016 meta-analysis of prognostic factors for seizure outcomes in patients with MRI-–negative temporal lobe epilepsy included a search of MEDLINE from 2000 to 2015.[23] Eighteen studies (total N=391 patients) were included with a mean or median follow-up of more than 1 year; however, only 5 studies (sample sizes not given) were included in the PET analysis. Seizure freedom was defined as freedom from any type of seizure or an Engel class I seizure outcome. Odds ratios and corresponding 95% confidence intervals (CIs) were calculated to compare the pooled proportions of seizure freedom between the groups who had localization of hypometabolism in the resected lobe vs those who did not. Table 2 shows summary results.

In 2015, Burneo et al published a recommendation report for the Program in Evidence-based Care (PEBC) and the PET steering committee of Cancer Care Ontario, which was based on a systematic review of studies of diagnostic accuracy and clinical utility of FDG-PET in the presurgical evaluation of adult and pediatric patients with medically intractable epilepsy.[24] The literature review included searches of the MEDLINE, EMBASE, and OVID databases from the years 1946 to 2013, society meeting abstracts,

practice guidelines, and the Cochrane database. Systematic reviews, RCTs, and observational studies that evaluated the use of FDG-PET in medically intractable epilepsy were eligible for inclusion. The reviewers included 39 observational studies (total N=2650 participants) in the qualitative review. Good surgical outcome was defined as Engel class I, II, or III, seizure-free, or significant improvement (<10 seizures per year and at least a 90% reduction in seizures from the preoperative year). Due to heterogeneity in patient populations, study designs, outcome measurements, and methods of PET interpretation, pooled estimates were not provided; however, ranges are displayed in Table 2.

A 2012 meta-analysis on predictors of long-term seizure freedom after surgery for frontal lobe epilepsy included articles found through a MEDLINE search for years 1990 through 2010 that had at least 10 participants and 48 months of follow-up.[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 findings did not predict seizure freedom.

A 2007 meta-analysis on the use of FDG-PET for preoperative evaluation of adults with temporal lobe epilepsy included 46 studies published between 1992 and 2006 and identified through MEDLINE.[26] Follow-up ranged from 3 to 144 months. Engel class I and II were defined as a good surgical outcome. The prognostic 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 value of PET was unclear. PET may not add value for patients well localized by ictal scalp electroencephalography and MRI.

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

Study	No. of Studies	N (Range)	Outcome	Estimate	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	Range: • 56%-90% overall (adults) • 63%-90% in temporal lobe epilepsy (adults)	No pooling		
	13	1064	Surgical prognostic accuracy (good surgical outcome)	Range: • 36%-89% (adults)	No pooling		
	6	690	Clinical decisions (influence decision making)	Range: • 53%-71% (adults) • 51%-95% (children)	No pooling		
Englot et al (2012)[25]	21[a]	1199[a]	Surgical 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 (2-117)	Surgical 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.

Clinical Utility

Systematic Reviews

The 2015 recommendation report by Burneo et al 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 EEGs, and ruled out an additional evaluation of the patient. Among pediatric patients who underwent FDG-PET, clinicians reported using the results to alter surgical decisions, classify symptomatic infantile spasms, and avoid invasive monitoring due to localizing information. The study results were not pooled due to heterogeneity among the study designs and patient populations (see Table 2).

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 were several retrospective studies that surveyed clinicians on the utility of FDG-PET in managing patients with epilepsy. In general, the clinicians reported that the information from FDG-PET was helpful in surgical management decisions. Only observational studies are available, most having small samples sizes with varying patient characteristics and definitions of good surgical outcomes.

Suspected Chronic Osteomyelitis

Clinical Validity

Systematic Reviews

In a 2013 systematic review of 9 studies (total N=299 patients), FDG-PET and PET with CT were found to be useful for suspected osteomyelitis in the foot of patients with diabetes.[28] 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 (AUROC) was 0.874.

In 2005, Termaat et al published a systematic review and meta-analysis of diagnostic imaging to assess chronic osteomyelitis.[29] Reviewers assessed 6 imaging approaches to chronic osteomyelitis, including FDG-PET and concluded that PET was the most accurate mode (pooled sensitivity, 96%; 95% CI, 88% to 99%; pooled specificity, 91%; 95% CI, 81% to 95%) for diagnosing chronic osteomyelitis. Leukocyte scintigraphy was adequate in the peripheral skeleton (sensitivity, 84%; 95% CI, 72% to 91%; specificity, 80%; 95% CI, 61% to 91%) but was inferior in the axial skeleton (sensitivity, 21%; 95% CI, 11% to 38%; specificity, 60%; 95% CI, 39% to 78%). The assessment of PET was based on 4 prospective, European studies published between 1998 and 2003 (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”[30]; (2) 22 trauma patients scheduled for surgery who had suspected metallic implant–associated infection[31]; (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[32]; and (4) 30 consecutive nondiabetic patients referred for possible chronic osteomyelitis.[33] The results appeared to be robust across fairly diverse clinical populations, which strengthen the conclusions.

Prospective Studies

In 2016, Rastogi et al 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.[34] Patients with suspected diabetic foot osteomyelitis (N=23) underwent radiographs, FDG-PET/CT, and contrast-enhanced MRI. Bone culture, which is considered the criterion standard, identified 12 of the 23 patients with osteomyelitis. The sensitivity, specificity, PPV, and NPV of FDG-PET/CT in diagnosing osteomyelitis were 83%, 100%, 100%, and 85%, respectively. The same measures for contrast-enhanced MRI were 83%, 64%, 71%, and 78%, respectively.

Clinical Utility

No studies were identified with evidence for the clinical utility of FDG-PET for diagnosing osteomyelitis. However, 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 2 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 in one of the systematic reviews and in the prospective study, FDG-PET and FDG-PET/CT were found to have better diagnostic capabilities than contrast-enhanced MRI and leukocyte scintigraphy in the peripheral skeleton.

Suspected Alzheimer Disease

This evidence review does not discuss PET tracers that bind to amyloid beta plaques (see review 6.01.55).

Clinical Validity

Systematic Reviews

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

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

Study (Year)	Dates	No. of Studies	N (Range)	Study Design	Outcome
Smailagic et al (2015)[35]	1999-2013	16	697 (19-94)	OBS	Diagnostic accuracy for predicting conversion to AD in those with MCI
Davison et al (2014)[36]	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)[37]	1990-2010	119	NR	OBS	Diagnostic accuracy for diagnosis of AD, differential diagnosis in dementia
Yuan et al (2009)[38]	2001-2005	6	280 (17-128)	OBS	Diagnostic accuracy for predicting conversion to AD in those with MCI
Matchar et al (2001)[39]	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: fluorine 18 fluorodeoxyglucose; MCI: mild cognitive impairment; NR: not reported; OBS: observational; PET: positron emission tomography.

A 2015 Cochrane review intended to determine the diagnostic accuracy of FDG-PET for detecting people with mild cognitive impairment (MCI) at baseline who would clinically convert to AD or other forms of dementia at follow-up.[35] Database searches were performed to January 2013. Included studies evaluated the diagnostic accuracy of FDG-PET to determine the conversion from MCI to AD or to other forms of dementia. Sixteen studies (total N=697 participants) were included in the qualitative review and 14 studies (n=421 participants) were included in the analysis. Because there are no accepted thresholds to define PET positivity and studies used mixed thresholds for diagnosis, reviewers used a hierarchical summary received operating characteristic (ROC) 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 were between 46% and 95% while the specificities were between 29% and 100%; however, a meta-analysis was precluded because of too few studies with small numbers of participants. Reviewers indicated that most studies were poorly reported, and the majority of selected studies had an unclear risk of bias, mainly for the reference standard and participant selection domains.

In a 2014 systematic review (quality assessment of included studies was not reported), Davison et al reported on studies on the diagnostic performance of FDG-PET and single-photon emission computed tomography identified through a MEDLINE search up to February 2013.[36] Three studies (197 patients) used histopathology as reference standard. In patients with or without a clinical diagnosis of AD, sensitivity was 84% and specificity was 74%; in patients with memory loss or dementia, sensitivity was 94% and specificity was approximately 70%; in patients undergoing evaluation for dementia, sensitivity was 94% and specificity was 73%. Precision estimates were not given. In 3 different studies (271 participants), the sensitivities and specificities of FDG-PET for distinguishing AD from Lewy body dementia ranged from 83% to 99% and from 71% to 93%, respectively. And in 2 studies (183 participants), for predicting conversion from MCI to AD, sensitivity and specificity of PET were 82% and 57% vs 78% and 67%, respectively.

Bloudek et al (2011) published a meta-analysis of diagnostic strategies for AD.[37] 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 AUROC, sensitivity, and specificity among all of the diagnostic methods for distinguishing AD from normal controls but had almost the lowest ROC comparing AD with non-AD demented controls (excluding MCI) due primarily to the low specificity in this group. Results are shown in Table 4.

A 2009 meta-analysis compared the abilities of FDG-PET, single-photon emission computed tomography, and structural MRI in order to predict patients' conversion from MCI to AD.[38] 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.

A 2001 technology assessment conducted for the Agency for Healthcare Research and Quality used decision-analysis modeling to examine whether the use of FDG-PET would improve health outcomes for diagnosis of AD in 3 clinical populations: patients with dementia, patients with MCI, and subjects with no symptoms but with a first-degree relative with AD.[39] For the review, a search was performed using MEDLINE, CINAHL, and the HealthSTAR databases from 1995 to 2001. Eighteen articles (total N=1018 participants) were included. 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 ROC method was used to calculate the pooled AUC 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.

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.[40] 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%.

Clinical Utility

In 2017, Motara et al assessed the accuracy of dual-trained radiologists and nuclear medicine physicians to diagnose the type of cognitive impairment based on FDG-PET/CT images. Records of patients who had undergone FDG-PET/CT because of cognitive impairment (AD, frontotemporal dementia, mixed dementia, and dementia with Lewy bodies) following a negative CT or MRI were reviewed (N=136).[41] Questionnaires were sent to the referring physicians to gather information on the final clinical diagnosis, usefulness of the PET/CT report, and whether the report impacted clinical management. Response rate was 72% (98/136) and mean patient follow-up was 471 days. For the diagnosis of AD, using the final clinical diagnosis as the reference standard, the sensitivity, specificity, PPV, and NPV were 87%, 97%, 93%, and 91%, respectively. Questionnaires received from the 98 physicians indicated that PET/CT: was useful (78%); had an impact on clinical management (81%); added confidence to the pretest clinical diagnosis (43%); reduced the need for further investigations (42%); changed the pretest clinical diagnosis (35%); and led to a change in therapy (32%).

Section Summary: Suspected Alzheimer Disease

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

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

Study	No. of Studies	N	Outcome	Estimate (95% CI)
Smailagic et al (2015)[35]	14	421	Diagnostic accuracy	• Sensitivity range: 25%-100% • Specificity range: 15%-100% • Pooled ROC (at median specificity) sensitivity: 76% (54% to 90%) • PLR: 4.03 (2.97 to 5.47) • NLR: 0.34 (0.15 to 0.75)
Davison et al (2014)[36]	3	197	Diagnostic accuracy, overall	• Sensitivity: 84% • Specificity: 74%
	2	183	Diagnostic accuracy, predicting conversion from MCI to AD	• Sensitivity range: 82%-57% • Specificity range: 78%-67%
	5	292	Diagnostic accuracy, differentiating	• Sensitivity range: 83%-92%

Study	No. of Studies	N	Outcome	Estimate (95% CI)
			AD and LBD	• Specificity range: 67%-93%
Bloudek et al (2011)[37]	20	NR	Diagnostic accuracy, overall	• 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)[38]	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)[39]	15	729	Diagnostic accuracy, pooled ROC	• 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: fluorine 18 fluorodeoxyglucose; LBD: Lewy body dementia; MCI: mild cognitive impairment; NLR: negative likelihood ratio; NR; not reported; PET: positron emission tomography; PLR: positive likelihood ratio; ROC: receiver operating characteristic.

Suspected Large Vessel Vasculitis

Clinical Validity

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 (Year)	Dates	No. of Studies	N (Range)	Study Design	Outcome
Lee et al (2016)[42]	Up to 2015	8	400 (21-93)	OBS	Diagnostic accuracy for GCA and TA
Soussan et al (2015)[43]	2000-2013	21	712 (18-93)	OBS	Diagnostic accuracy for GCA; assessment of disease activity in TA
Puppo et al (2014)[44]	1999-2014	19	977 (8-304)	OBS	Diagnostic accuracy for GCA (qualitative vs semiquantitative criteria)
Treglia et al (2011)[45]	Up to 2011	32	604	OBS	Diagnostic accuracy for GCA and TA; assessment of disease activity; monitor treatment response
Besson et al (2011)[46]	Up to 2011	14	Unclear	OBS	Diagnostic accuracy for GCA

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

Lee et al (2016) performed a meta-analysis of the diagnostic accuracy of FDG-PET or PET/CT for LVV.[42] The search included studies indexed in PubMed, EMBASE, or Cochrane Library and published before February 2015 that used American College of Rheumatology (ACR) classification as the reference standard diagnosis. Eight studies were (total N=400 participants) identified for inclusion. Five studies included participants with both giant cell arteritis (GCA) and Takayasu arteritis (TA) while three included only GCA. Five studies evaluated FDG-PET and three evaluated FDG-PET/CT. Pooled estimates of sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were calculated using a random-effects model and are shown in table 6. Interpretation of these results is limited by the use of ACR as the reference standard and the varying levels of disease activity in selected studies.

In 2015 a literature review on the role of FDG-PET in the management of LVV, focused on 3 issues: determining the different FDG-PET criteria for the diagnosis of vascular inflammation; establishing the performance of FDG-PET for the diagnosis of large-vessel inflammation in GCA patients; and defining the performance of FDG-PET to evaluate the disease inflammatory activity in patients with TA.[43] The MEDLINE, Cochrane Library, and EMBASE databases were searched for articles that evaluated the value of FDG-PET in LVV, from January 2000 to December 2013. Inclusion criteria were ACR criteria for GCA or TA, definition of a PET positivity threshold, and more than 4 cases included. The sensitivity and specificity of FDG-PET for the diagnosis of large vessel inflammation were calculated from each selected

study and then pooled for meta-analysis with a random-effects model. Disease activity was assessed with the National Institutes of Health Stroke Scale[47] or another activity assessment scale. Twenty-one studies (413 patients, 299 controls) were included in the systematic review. FDG-PET showed FDG vascular uptake in 70% (288/413) of patients and 7% (22/299) of controls. Only vascular uptake equal to or higher than the liver uptake differed significantly between GCA plus TA patients and controls (p<0.001). A summary of the results is shown in Table 6. FDG-PET showed good performances in the diagnosis of large-vessel inflammation, with higher accuracy for diagnosing GCA patients than for detecting activity in TA patients. Although a vascular uptake equal to or higher than the liver uptake appears to be a good criterion for the diagnosis of vascular inflammation, further studies are needed to define the threshold of significance as well as the clinical significance of the vascular uptake.

A 2014 systematic review included studies of FDG-PET in GCA comparing the diagnostic performance of qualitative and semiquantitative methods of FDG-PET interpretation.[44] Reviewers selected 19 studies (442 cases, 535 controls) found in PubMed or Cochrane Library through April 2014. The included studies had various reference standards. Ten used qualitative FDG uptake criteria to characterize inflammation, six used semiquantitative criteria, and three used both. Meta-analyses were not performed. Overall, qualitative methods were more specific, but less sensitive, than semiquantitative methods. Diagnostic performance varied by vessel and by thresholds (cutoffs) for positivity. Results are shown in Table 6.

In 2011, Treglia et al published a systematic review of PET and PET/CT in patients with LVV.[45] Reviewers searched MEDLINE and Scopus for publications through April 2011 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, 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 and meta-analysis of FDG-PET for patients with suspected GCA based on a search of MEDLINE, EMBASE, and the Cochrane Library up to November 2011.[46] 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 on Use of FDG-PET for Large Vessel Vasculitis

Study	No. of Studies	N	Outcome	Estimate (95% CI)
Lee et al (2016)[42]	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)[43]	4	233	Diagnostic accuracy for GCA	• Sensitivity: 89.5% (78.5% to 96.0%) • Specificity: 97.7% (CI, 94% to 99%)

Study	No. of Studies	N	Outcome	Estimate (95% CI)
				• PLR: 28.7 (11.5; 71.6) • NLR: 0.15 (0.07; 0.29)
	7	237	Diagnostic accuracy for disease activity in TA	• Sensitivity: 87% (78% to 93%) • Specificity: 73% (63% to 81%) • PLR: 4.2 (1.5 to 12) • NLR: 0.2 (0.1 to 0.5)
Puppo et al (2014)[44]	10	633	Diagnostic accuracy for GCA using qualitative criteria	• Sensitivity range: 56%-77% • Specificity range: 77%-100% • PPV range: 93%-100% • NPV range: 70%-82%
	6	282	Diagnostic accuracy for GCA using semiquantitative criteria	• Sensitivity range: 58%-90% • Specificity range: 42%-95% • PPV range: 79%-89% • NPV range: 95%-98%
	3	72	Diagnostic accuracy for GCA using mixed qualitative and semiquantitative criteria	• Sensitivity range: 65%-100% • Specificity range: 45%-100%
Treglia et al (2011)[45]	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)[46]	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) • Accuracy: 84% (76% to 90%)

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.

Clinical Utility

No studies were identified with evidence for clinical utility.

Section Summary: Suspected Large Vessel Vasculitis

There have been several systematic reviews of 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 against the true reference standard (biopsy or angiography) were rare. There are no consensus criteria to define the presence of vascular inflammation by FDG-PET in LVV, and different parameters with visual and semiquantitative methods have been reported. Studies demonstrating changes in management based on PET results or improvements in clinical outcomes are lacking.

Diverse Noncardiac or Nononcologic Conditions

Numerous systematic reviews have described the use of PET in patients with carotid stenosis[48]; inflammatory diseases[49,50]; fever of unknown origin[51-53]; hyperinsulinemic hypoglycemia[54,55]; spinal infections[56]; mycobacterium infection[57]; Creutzfeldt-Jakob disease[58]; vascular prosthetic graft infection[59]; prosthetic infection after knee or hip arthroplasty[60]; inflammatory bowel disease[61]; atypical parkinsonism[62]; and Huntington disease.[63] 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 connect the PET results in individual patients to improved clinical outcomes.

A 2011 systematic review addressed the use of PET in evaluating disease activity in patients with sarcoidosis.[64] It did not include a quality assessment of individual studies, a critical feature of a well-

conducted systematic review. Only 3 small studies of nine reviewed included data from a comparator imaging modality; thus, conclusions about comparative diagnostic performance cannot be reached.

A 2008 systematic review of FDG-PET to diagnose prosthetic joint infection following hip or knee replacement reported on 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.[65] Reviewers noted significant heterogeneity among the 11 studies included in the analysis. Differences in performance were based on the location of prostheses (hip vs knee) and whether filtered back projection or iterative reconstruction was used. This meta-analysis and a 2009 study on the same clinical issue found that the specificity of PET was significantly greater for hip prostheses than for knee prostheses.[66] The articles also noted that these results were based on the use of PET alone. CT is generally not useful in evaluating potential infections around joint prostheses because of the artifacts caused by the metallic implants, so additional research would be needed on combined PET/CT. The 2009 study compared the accuracy of PET with a triple-phase scan and with white blood cell imaging.

Section Summary: Diverse Noncardiac and Nononcologic Conditions

There are systematic reviews for the use of FDG-PET or FDG-PET/CT for the diagnosis or management of carotid stenosis, various inflammatory and immune-mediated diseases, fever of unknown origin, and various infections. However, studies included in the reviews are mostly small, retrospective, and lacked standard definitions of PET interpretation and positivity. Few studies compared PET with other diagnostic modalities and no studies 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 5 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 both 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 2 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 the second meta-analysis from 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 addressing 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 connect the PET results in individual patients to improved clinical outcomes. Additional studies are needed to demonstrate FDG-PET results can change management, and therefore improve patient outcomes to determine that FDG-PET is a clinically useful test. The evidence is insufficient to determine the effect of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

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[67]	2004: reaffirmed	PET imaging not recommended for routine use in diagnostic evaluation of dementia (LOR: moderate clinical certainty)
Early detection of dementia[68]	2003: reaffirmed	Not addressed
Diagnosis of new-onset PD[69]	2006: reaffirmed 2013; retired	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[70]	2006: UIP	Not addressed

FDG: fluorodeoxyglucose; LOR: level of recommendation; PD: Parkinson disease; PET: positron emission tomography; UIP: update in progress.

American Academy of Orthopaedic Surgeons

The American Academy of Orthopaedic Surgeons published evidence-based, consensus guidelines in 2010.[71] 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)[72]	2016	• 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[73]	2001, reaffirmed in 2004	PET imaging not recommended for routine use in diagnostic evaluation of dementia (LOR: moderate clinical certainty)
Early detection of dementia[73]	2001, reaffirmed in 2003, UIP	Not addressed
Diagnosis of new onset-PD[73]	2006: reaffirmed in 2013; retired in 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[73]	2006: UIP	Not addressed
Dementia and movement disorders[74]	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 TKA[75]	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[76]	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[77]	2014	Usually not appropriate
Fever without source – child[78]	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[79]	2012	Usually not appropriate

AD: Alzheimer disease; CJD: Creutzfeldt-Jakob disease; CT: computed tomography; DM: diabetes mellitus; FDG: fluorodeoxyglucose; FTD: frontotemporal dementia; HD: Huntington disease; LBD: Lewy body disease; LOR: level of recommendation; PD: Parkinson disease; PET: positron emission tomography; TKA: total knee arthroplasty; UIP: update in progress.

Infectious Diseases Society of America

The Infectious Diseases Society of America (IDSA) published evidence-based, consensus guidelines on the diagnosis and treatment of native vertebral osteomyelitis in adults in 2015.[80] 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 published evidence-based, consensus guidelines on the diagnosis and management of prosthetic joint infections in 2013.[81] The guidelines concluded that PET should not be routinely used to diagnoses

prosthetic joint infection (Strength of recommendation: B [based on moderate evidence]; Quality of evidence: III [expert opinion and descriptive studies]).

IDSA published evidence-based, consensus guidelines on the diagnosis and treatment of diabetic foot infections in 2012.[82] The guidelines concluded that the role of FDG-PET in evaluating a diabetic foot infection has not been established.

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

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

MEDICARE NATIONAL COVERAGE

In 2004, the Centers for Medicare & Medicaid Services (CMS) made public its final decision memorandum announcing a positive national coverage decision for a subset of patients "with a recent diagnosis of dementia and documented cognitive decline of at least 6 months, who meet diagnostic criteria for both [Alzheimer disease] and frontotemporal dementia, who have been evaluated for specific alternative neurodegenerative diseases or causative factors, and for whom the cause of the clinical symptoms remains uncertain."[83] For its reconsideration, CMS requested an updated Agency for Healthcare Research and Quality assessment, which concluded that no new publications provided direct evidence to evaluate the use of PET to either differentiate among different types of dementia or to identify those patients with mild cognitive impairment who were at greatest risk to progress to AD.[84] Additionally, CMS considered a consensus report by the Neuroimaging Work Group of the Alzheimer's Association[85] and proceedings of an expert panel discussion of neuroimaging in AD, convened by the National Institute of Aging and Medicare.[86]

The national coverage determination for FDG-PET for dementia and neurodegenerative diseases (220.6.13) states that:

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

Specific requirements for each indication are clarified in the document.[87]

The national coverage determination for FDG-PET for infection and inflammation (220.6.16) states that:

> "The CMS is continuing its national noncoverage of FDG PET for the requested indications. Based upon our review, CMS has determined that the evidence is inadequate to conclude that FDG PET for chronic osteomyelitis, infection of hip arthroplasty, and fever of unknown origin improves health outcomes in the Medicare populations, and therefore has determined that FDG PET for chronic osteomyelitis, infection of hip arthroplasty, and fever of unknown origin is not reasonable…."[88]

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			
NCT02084147	PET-MRI: Evaluation, Optimization and Clinical Implementation	530	Sep 2017
NCT00811122	Biodistribution of 11C-PIB PET in Alzheimer's Disease, Frontotemporal Dementia, and Cognitively Normal Elderly	30	Apr 2018
NCT03022968	Tau Brain Imaging in Typical and Atypical Alzheimer's Disease	24	Sep 2018
NCT00194298	FDG-PET Imaging in Complicated Diabetic Foot	240	Jan 2020

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02771483	Improving the Diagnosis and Prognostication of Giant Cell Arteritis through the Novel Use of Positron Emission Tomography (PET), Microbiological and Immune Biomarkers	50	Apr 2027
Unpublished			
NCT00329706	Early and Long-Term Value of Imaging Brain Metabolism	710	Jan 2017
NCT01550484[a]	An Open Label, Multicenter Study, Evaluating the Safety and Efficacy of 18F-AV-133 PET Imaging to Identify Subjects With Dopaminergic Degeneration Among Subjects Presenting to a Movement Disorders Specialty Clinic With an Uncertain Diagnosis	170	Mar 2016

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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CODES

Codes	Number	Description
CPT	78608	Brain imaging, PET, metabolic evaluation
	78609	Brain imaging, PET, perfusion evaluation
	78811-78813	Positron emission tomography (PET) imaging code range
	78814-78816	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging code range
HCPCS	A9552	Fluorodeoxyglucose F-18 FDG, diagnostic, per study dose, up to 45 millicuries
ICD-10-CM	G40.001-G40-919	Epilepsy and recurrent seizures code range
	M86.30-M86.69	Chronic osteomyelitis code range
ICD-10-PCS	C030KZZ	Nuclear medicine, central nervous system, positron emission tomography (PET), brain, Fluorine 18 (F-18)
		There are no specific codes for PET of the musculoskeletal system. The following codes might be used.
	CP21YZZ, CP22YZZ, CP23YZZ, CP24YZZ, CP26YZZ, CP27YZZ, CP28YZZ, CP29YZZ, CP2BYZZ, CP2CYZZ, CP2DYZZ, CP2FYZZ, CP2GYZZ, CP2HYZZ, CP2JYZZ, CP2YYZZ	Nuclear medicine, musculoskeletal system, tomographic nuclear medicine imaging, other radionuclide, codes by body part
Type of Service	Radiology	
Place of Service	Inpatient Outpatient Physician's Office	

POLICY HISTORY

Date	Action	Description
12/01/95	Add to Radiology section	New policy
01/30/98	Replace policy	Reviewed with changes; new CPT codes
07/10/98	Replace policy	Revised policy; updated regulatory status to PET
07/10/99	Replace policy	Original policy on PET scans put into 2 policies; 6.01.06 noncardiac application and 6.01.20 cardiac applications; recommendation for noncardiac applications of PET are unchanged
08/18/00	Replace policy	Revised because cardiac and oncologic applications of PET scans now addressed in separate policies, 6.01.20 and 6.01.26, respectively. Policy statement regarding remaining applications, unchanged
12/17/03	Replace policy	Policy updated. Policy statements added regarding musculoskeletal uses (investigational); for remaining applications, policy statements unchanged.
11/09/04	Replace policy	Policy updated with CMS decision regarding PET scans for dementia; policy statement unchanged, still consider PET for dementia as investigational

12/14/05	Replace policy	Policy updated; search for systematic review, meta-analyses, and decision analyses found no sources that would change policy positions. HCPCS coding updated.
04/17/07	Replace policy	Policy updated with literature search; reference numbers 17-22 added. Policy statements changed: chronic osteomyelitis added as "may be considered medically necessary" and giant cell arteritis added as "investigational." Code table updated.
08/13/09	Replace policy	Policy updated with literature search; references 23-28 added. Two additional dementia subtypes added to policy statement (frontotemporal dementia and dementia with Lewy Bodies); policy statements otherwise unchanged.
11/11/10	Replace policy	Policy updated with literature search; minor changes to policy statements (investigational indication for schizophrenia moved from dementias to psychiatric diseases and disorders; "vasculitis" added to investigational "other" category). References 29-36 added
12/08/11	Replace policy	Policy updated with literature search. "Non-cardiac, non-oncologic" added to title. Mycobacterium infection and inflammatory bowel disease added as investigational indications. Regulatory status information moved to Description section. Rationale rewritten. References 19-21, 26-28, and 31-34 added; other references renumbered or removed.
02/14/13	Replace policy	Policy updated with literature search; Sarcoidosis added as investigational indication, no other changes to policy statement
02/13/14	Replace policy	Policy updated with literature search on January 23, 2014; reference 12 added; no changes to policy statement
02/12/15	Replace policy	Policy updated with literature review through January 27, 2015; references 13-14, 19, 25, 28-29, 38-40, 42, 47-49, and 51-60 added; reference 50 updated. Vascular prosthetic graft infection, fever of unknown origin, and inflammation of unknown origin added as investigational indications. Acanthocytosis and assessment of cerebral blood flow in newborns revised but no other changes to policy statements.
09/10/15	Replace policy	Policy updated with literature review through July 23, 2015; references 13 and 26 added. Policy statements unchanged.
09/08/16	Replace policy	Policy updated with literature review through July 29, 2016; references 1-15, 19-21, 32, 39, 44, and 58 added. Policy statements unchanged. Added "Fluorodeoxyglucose F 18" to the title and "FDG" to the investigational statement.
09/14/17	Replace policy	Policy updated with literature review through July 25, 2017; references 27, 34, 40-41, 53, and 62 added. Policy statements unchanged. Policy title changed for consistency with terminology, "Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography."