FEP 6.01.06 Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography

Effective Date: January 15, 2018

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

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

FDA 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 and, in August 2011, issued similar Current Good Manufacturing Practice guidance for small businesses compounding radiopharmaceuticals. 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.

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.)

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.

**POLICY STATEMENT**

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

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

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 1.

Table 1. Practice Parameters on Diagnosis of Dementia

<table>
<thead>
<tr>
<th>Practice Parameter</th>
<th>Date</th>
<th>PET Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of dementia</td>
<td>2004: reaffirmed</td>
<td>PET imaging not recommended for routine use in diagnostic evaluation of dementia (LOR: moderate clinical certainty)</td>
</tr>
<tr>
<td>Early detection of dementia</td>
<td>2003: reaffirmed</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Diagnosis of new-onset PD</td>
<td>2006: reaffirmed; 2016</td>
<td>Evidence insufficient to support or refute FDG-PET as a means of distinguishing PD from other parkinsonian syndromes</td>
</tr>
<tr>
<td>Evaluation of depression, psychosis, and dementia in PD</td>
<td>2006: UIP</td>
<td>Not addressed</td>
</tr>
</tbody>
</table>

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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 2.

Table 2. Appropriateness Criteria for Miscellaneous Indications of FDG-PET/CT

<table>
<thead>
<tr>
<th>Appropriateness Criteria</th>
<th>Last Reviewed</th>
<th>FDG-PET/CT Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected osteomyelitis, septic arthritis, or soft tissue infection (excluding spine and diabetic foot)72</td>
<td>2017</td>
<td>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.”</td>
</tr>
<tr>
<td>Diagnosis of dementia73</td>
<td>2001, reaffirmed in 2004</td>
<td>PET imaging not recommended for routine use in diagnostic evaluation of dementia (LOR: moderate clinical certainty)</td>
</tr>
<tr>
<td>Early detection of dementia74</td>
<td>2001, reaffirmed in 2003, UIP</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Diagnosis of new onset-PD73</td>
<td>2006: reaffirmed in 2013; retired in 2016</td>
<td>Evidence insufficient to support or refute FDG-PET as a means of distinguishing PD from other parkinsonian syndromes</td>
</tr>
<tr>
<td>Evaluation of depression, psychosis, and dementia in PD73</td>
<td>2006: UIP</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Dementia and movement disorders74</td>
<td>2016</td>
<td>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</td>
</tr>
<tr>
<td>Imaging after TKA70</td>
<td>2017</td>
<td>Usually not appropriate for routine follow-up of asymptomatic patient, in work-up for suspected periprosthetic infection, or for evaluation of prosthetic loosening</td>
</tr>
<tr>
<td>Seizures and epilepsy75</td>
<td>2014</td>
<td>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</td>
</tr>
<tr>
<td>Crohn disease77</td>
<td>2014</td>
<td>Usually not appropriate</td>
</tr>
<tr>
<td>Fever without source – child78</td>
<td>2015</td>
<td>May be appropriate. This procedure should not be used as the initial study. Consider if extensive clinical and imaging work-up is negative.</td>
</tr>
</tbody>
</table>

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Suspected osteomyelitis of the foot in patients with DM

<table>
<thead>
<tr>
<th>Year</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Usually not appropriate</td>
</tr>
</tbody>
</table>

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. 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. 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 published evidence-based, consensus guidelines on the diagnosis and treatment of diabetic foot infections in 2012. 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

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


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16. 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. PMID 9666641

17. 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. PMID 9666641


20. 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. PMID 9666641

21. 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. PMID 9666641


42. 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


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POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2012</td>
<td>New Policy</td>
<td></td>
</tr>
<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search; Sarcoidosis added as not medically necessary indication, no other changes to policy statement.</td>
</tr>
<tr>
<td>June 2014</td>
<td>Update Policy</td>
<td>Policy update with literature review. Reference 12 added; no changes to policy statement.</td>
</tr>
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