BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 6.01.06 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 (Genitourinary)
6.01.51 - Interim Positron Emission Tomography Scanning in Oncology to Detect Early Response During Treatment
6.01.55 - Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease

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

Description

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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.

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

A variety of tracers are used for PET scanning, including oxygen 15, nitrogen 13, carbon 11, and fluorine 18. The radiotracer most commonly used in oncology imaging has been fluorine 18, coupled with fluorodeoxyglucose (FDG), which has a metabolism related to glucose metabolism. While FDG has traditionally been used in cancer imaging, it potentially has many other applications.

OBJECTIVE

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

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

This policy does not cover the use of fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) for diagnosis or evaluation of Alzheimer's disease or other dementias. See related evidence review 6.01.55 for Alzheimer's disease indications for FDG. This policy also does not cover oncologic or cardiovascular uses of FDG-PET. See related evidence reviews 6.01.26 and 6.01.51 for oncologic indications and 6.01.20 for cardiac indications for FDG.

BENEFIT APPLICATION

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

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 the FDA through the 510(k) process. These systems are intended to aid in detecting, localizing, diagnosing, staging, and restaging of lesions, tumors, disease, and organ function for the evaluation of diseases, and disorders such as, but not limited to, cardiovascular disease, neurologic disorders, and cancer. The images produced by the system can aid in radiotherapy treatment planning and interventional radiology procedures.

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

In December 2009, the FDA issued guidance for Current Good Manufacturing Practices for PET drug manufacturers.[1,] and, in August 2011, issued similar Current Good Manufacturing Practices guidance for small businesses compounding radiopharmaceuticals.[2,] An additional final guidance document, issued in December 2012, required all PET drug manufacturers and compounders to operate under an approved new drug application (NDA) or abbreviated NDA, or investigational new drug application, by December 12, 2015.[3,]

In 1994, the FDG radiotracer was originally approved by the FDA through the NDA (20-306) process. The original indication was for "the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures." Added indications in 2000 were for "Assessment of glucose metabolism to assist in the evaluation of malignancy..." and "Assessment of patients with coronary artery disease and left ventricular dysfunction...."

Multiple manufacturers have approved NDAs for FDG.[4,]

See related evidence reviews 6.01.26 and 6.01.51 for oncologic indications and 6.01.20 for cardiac indications for FDG. See related evidence review 6.01.55 for Alzheimer's disease indications for FDG.

RATIONALE

Summary of Evidence

For individuals with epileptic seizures who are candidates for surgery who undergo fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) , the evidence includes systematic reviews (following the publication of 3 TEC Assessments). Relevant outcomes are symptoms, change in disease status, functional outcomes, health status measures, quality of life (QOL) , hospitalizations, medication use, and resource utilization. The TEC Assessments and Program in Evidence-based Care positron emission tomography (PET) recommendation report all concluded that FDG-PET accurately localizes the seizure focus compared with appropriate reference standards. A recent systematic review suggested it was difficult to discern the incremental value of FDG-PET in patients who have foci well localized by ictal scalp electroencephalography (EEG) and magnetic resonance imaging (MRI). The evidence on whether FDG-PET has a predictive value for a good surgical outcome is mixed. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with suspected chronic osteomyelitis who receive FDG-PET, the evidence includes meta-analyses and a prospective study published after the meta-analyses. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, functional outcomes, QOL, and hospitalizations. One systematic review and meta-analysis from 2013 of 9 studies revealed that FDG-PET and FDG-PET plus computed tomography (CT) were useful for diagnosing suspected osteomyelitis in the foot of patients with diabetes. The results of another meta-analysis showed that FDG-PET was the most accurate mode (pooled sensitivity, 96%; pooled specificity, 91%) for diagnosing chronic osteomyelitis. The results appear to be robust across fairly diverse clinical populations, which strengthen the conclusions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with suspected large vessel vasculitis (LVV) who receive FDG-PET, the evidence includes 6 systematic reviews of observational studies and an observational study. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, morbid events, QOL, 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 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with diverse noncardiac or nononcologic conditions (eg, central nervous system, pulmonary, and musculoskeletal diseases) who receive FDG-PET, the evidence includes several systematic reviews. Relevant outcomes are overall survival, symptoms, change in disease status, functional outcomes, health status measures, QOL, hospitalizations, medication use, and resource utilization. Many studies cited in the reviews were small, retrospective, and published in the 1990s to early 2000s. Further, many studies did not directly compare a modality with another in the same patient group, nor did they correlate PET results in individual patients with improved clinical outcomes. Additional studies are needed to demonstrate that FDG-PET results can change management, and therefore improve patient outcomes to support the utility of FDG-PET. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

American Academy of Orthopaedic Surgeons

The American Academy of Orthopaedic Surgeons (AAOS) (2019) published evidence-based, consensus guidelines on the diagnosis and prevention of periprosthetic joint infections.[66,]The AAOS recommendation regarding fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) is that there is limited strength of evidence supporting the use of FDG-PET/computed tomography (CT) to aid in the diagnosis of periprosthetic joint infections. The strength of the recommendation was rated as "limited," which was described as "Evidence from 2 or more 'Low' quality studies with consistent findings or evidence from a single 'Moderate' quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention."

American College of Radiology

Evidence and consensus-based appropriateness criteria from the American College of Radiology are summarized in Table 1.

Table 1. Appropriateness Criteria for Miscellaneous Indications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

Appropriateness Criteria	Last Reviewed	FDG-PET/CT Criteria
Suspected osteomyelitis, septic arthritis, or soft tissue infection (excluding spine and diabetic foot) [67,]	2022	May be appropriate for suspected osteomyelitis; may be appropriate for suspected osteomyelitis or soft tissue infection with implanted extra-articular surgical hardware; may be appropriate for suspected septic arthritis with arthroplasty or other implanted intra-articular surgical hardware.
Movement Disorders and Neurodegenerative Diseases[68,]	2019	May be appropriate as initial imaging for rapidly progressive dementia, suspected CJD; usually not appropriate for chorea, suspected HD; may be appropriate for initial imaging of parkinsonian syndromes; usually not appropriate for initial imaging of suspected neurodegeneration with brain iron accumulation; usually not appropriate for initial imaging of suspected motor neuron disease
Dementia and movement disorders[69,]	2016; revised 2019	May be appropriate in patients with possible or probable AD and to differentiate suspected FTD, LBD, CJD, or vascular dementia;

		usually not appropriate in patients with suspected HD, clinical features of PD or hemochromatosis, or motoneuron disease
Imaging after total knee arthroplasty[68,]	2023	Usually not appropriate for routine follow-up of asymptomatic patients, in work-up for suspected periprosthetic infection, for evaluation of prosthetic loosening, or suspected periprosthetic or hardware fracture
Seizures and epilepsy[70,]	2014; revised 2019	Usually appropriate for surgical planning in known seizure disorder; usually not appropriate for new-onset seizure, whether unrelated to trauma or with a history of trauma; may be appropriate (disagreement) for known seizure disorder with unchanged seizure semiology; may be appropriate for known seizure disorder with change in seizure semiology or new neurologic deficit or no return to previous neurologic baseline; may be appropriate (disagreement) for known seizure disorder with a history of trauma
Crohn disease[71,]	2014; revised 2019	Usually not appropriate
Fever without source - child[68,]	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[72,]	2012; revised 2019	Usually not appropriate for initial imaging. May be appropriate for soft-tissue swelling with or without ulcer, suspected osteomyelitis or early neuropathic arthropathy changes of the foot in patients with DM, suspected osteomyelitis of the foot in patients with DM with or without neuropathic arthropathy, and additional imaging following radiographs.
Noncerebral Vasculitis[73,]	2021	Usually appropriate for initial imaging of suspected LVV (FDG-PET/CT). Usually not appropriate for initial imaging of suspected medium vessel vasculitis.

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

Infectious Diseases Society of America

The Infection Diseases Society of America (IDSA) and the Pediatric Infectious Diseases Society (2021) published an evidence-based guidelines on acute hematogenous osteomyelitis in children.[74,] Studies that validate the utility of FDG-PET for diagnosing pediatric osteomyelitis were listed as a future research need.

The IDSA (2015) published evidence-based, consensus guidelines on the diagnosis and treatment of native vertebral osteomyelitis in adults.[75,] The guidelines stated that PET "is highly sensitive for detecting chronic osteomyelitis. A negative PET scan excludes the diagnosis of osteomyelitis, including native vertebral osteomyelitis, as the sensitivity of the test is expected to be very high in view of the high concentration of red marrow in the axial skeleton."

The IDSA (2013) published evidence-based, consensus guidelines on the diagnosis and management of prosthetic joint infections.[76,] The guidelines concluded that PET should not be routinely used to diagnose prosthetic joint infection (strength of recommendation: B [based on moderate evidence]; quality of evidence: III [expert opinion and descriptive studies]). These guidelines have now been archived and replaced by an endorsement of the clinical practice guidelines on the diagnosis and prevention of periprosthetic joint infections issued by AAOS (2019) described above.

The IDSA (2012) published evidence-based, consensus guidelines on the diagnosis and treatment of diabetic foot infections.[77,] The guidelines concluded that the role of FDG-PET in evaluating a diabetic foot infection has not been established. These guidelines have been archived with an update in development.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

"The CMS [Centers for Medicare and Medicaid Services] 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..."[78,]

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2012	New policy	
June 2013	Replace policy	Policy updated with literature search; Sarcoidosis added as not medically necessary indication, no other changes to policy statement.
June 2014	Replace policy	Policy update with literature review. Reference 12 added; no changes to policy statement.
June 2015	Replace policy	Policy updated with literature review; 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 not medically necessary indications. Acanthocytosis and assessment of cerebral blood flow in newborns revised but no other changes to policy statements.
December 2016	Replace policy	Policy updated with literature review; 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.
December 2017	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.,
December 2018	Replace policy	Policy updated with literature review through July 10, 2018; references 28 and 72 added; reference 18 updated. Policy statements unchanged.
December 2019	Replace policy	Policy updated with literature review through July 8, 2019; references added. Policy statements unchanged.
December 2020	Replace policy	Policy updated with literature review through July 24, 2020; references added. Policy statements unchanged.
December 2021	Replace policy	Policy updated with literature review through August 31, 2021; references added. Alzheimer's disease information removed and added to policy 6.01.55. Policy statements regarding remaining applications unchanged.
December 2022	Replace policy	Policy updated with literature review through September 7, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.
December 2023	Replace policy	Policy updated with literature review through August 24, 2023; no references added. Policy statements unchanged.