BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 6.01.55 Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease

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Related Policies:

2.04.14 - Evaluation of Biomarkers for Alzheimer Disease
6.01.06 - Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography

Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease

Description

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Alzheimer disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Because clinical diagnosis can be difficult, particularly early in the course of the disease or with atypical dementia, there has been considerable interest in developing biomarkers for AD that can be imaged through positron emission tomography (PET).

Demonstration of amyloid beta plaque is a requirement for the diagnosis of definite AD, but amyloid beta plaques may also be present in individuals without dementia, patients with mild or subjective cognitive impairment who may or may not progress to dementia, and patients with other types of dementia. Conversely, they may be absent in a substantial proportion of patients with clinical features of AD.[6,7,8,]

18-F fluorodeoxyglucose PET (18-F FDG PET) quantifies brain function by measuring glucose levels. Through identifying distinct regions of hypometabolism, FDG-PET is proposed as a method to distinguish AD from other dementias, especially in patients with atypical presentations (eg, younger age).[9,]

OBJECTIVE

The objective of this evidence review is to evaluate whether imaging with PET and FDG-PET, as an adjunct to clinical diagnosis, and whether imaging with PET in individuals who are being considered for, or being treated with, amyloid beta plaque-targeting therapy, improve the net health outcome in individuals with mild cognitive impairment or suspected Alzheimer disease.

POLICY STATEMENT

Amyloid beta imaging with positron emission tomography (PET) to predict conversion to Alzheimer disease is considered **investigational**.

Amyloid beta imaging with PET as an adjunct to clinical diagnosis in individuals with dementia is considered **investigational**.

Amyloid beta imaging with PET to select individuals with mild cognitive impairment or mild dementia due to Alzheimer disease for amyloid beta targeting plaque-therapy is considered **investigational**.

Amyloid beta imaging with PET to evaluate individuals with mild cognitive impairment or mild dementia due to Alzheimer disease for continuation of amyloid beta plaque-targeting therapy is considered **investigational**.

PET Imaging with fluorine 18 fluorodeoxyglucose (FDG-PET) as an adjunct to clinical diagnosis in individuals with dementia is considered **investigational**.

All other uses of amyloid beta imaging with PET are considered **investigational**.

POLICY GUIDELINES

This policy does not currently include tau PET imaging.

FDG-PET for individuals with suspected AD, previously included in Policy 6.01.06, was added to this policy in October 2021.

BENEFIT APPLICATION

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

FDA REGULATORY STATUS

Radiopharmaceuticals for Positron Emission Tomography Imaging

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.

Amyvid, Vizamyl™, and Neuraceq (Table 1) are approved by the FDA "for PET imaging of the brain to estimate amyloid beta neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline."[15,16,17,]

In 1994, the fludeoxyglucose (FDG) F18 radiotracer was originally approved by the FDA through the New Drug Application (NDA) process (NDA20306). 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...." FDA approval of FDG does not include the evaluation of patients with cognitive decline. Multiple manufacturers have approved NDAs for FDG.

The prescribing information for all 3 agents used for amyloid beta imaging states:

- The objective of amyloid beta image interpretation "is to estimate beta-amyloid neuritic plaque density in brain gray matter, not to make a clinical diagnosis."
- A positive amyloid beta scan "does not establish the diagnosis of AD or other cognitive disorder."
- A negative amyloid beta scan "indicates sparse to no neuritic plaques, and is inconsistent with a neuropathologic diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD."
- Florbetapir, florbetaben, and flutemetamol are not intended for use in "predicting development of dementia or other neurological condition" or for "monitoring responses to therapies."

Table 1. Radioactive Tracers Approved by the FDA for Amyloid Beta PET Imaging in Patents with Cognitive Impairment

Agent	Trade Name	Manufacturer	NDA	Approved
florbetapir F18	Amyvid	Avid Radiopharmaceuticals (subsidiary of Eli Lilly)	202008	2012
flutemetamol F18	Vizamyl	GE Healthcare	203137	2013
florbetaben F18	Neuraceq	Piramal Life Sciences	204677	2014

FDA: U.S. Food and Drug Administration; NDA: new drug application PET: positron emission tomography.

RATIONALE

Summary of Evidence

For individuals who have mild cognitive impairment (MCI) who receive amyloid beta imaging with positron emission tomography (PET) to predict conversion to Alzheimer disease (AD), the evidence includes studies on diagnostic accuracy and a randomized controlled trial (RCT) that evaluated changes in diagnosis and management. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, and quality of life. Studies have been conducted to evaluate the diagnostic accuracy of amyloid beta PET in patients with MCI, using conversion to probable AD as a reference standard. Systematic reviews of these studies have concluded that limited data, varying sensitivity and specificity, and risk of bias limited confidence in conclusions. In a more recent prospective study of 224 individuals with MCI, the hazard ratio for conversion to probable AD at 3 years in patients with a baseline positive amyloid beta PET scan was 2.51 (95% CI, 1.57 to 3.99; p <.001), with a NPV of 77%. Direct evidence of improved health outcomes with this technology is lacking. A RCT tested immediate versus delayed reporting of amyloid beta test results for patients with MCI and AD. No differences between the groups were found for health outcomes, although the study was not powered for these outcome measures. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have dementia who receive amyloid beta imaging with PET as an adjunct to clinical diagnosis, the evidence includes studies on diagnostic accuracy and a RCT that evaluated changes in diagnosis and management. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, and quality of life. One possible use of amyloid beta testing is as an adjunct to clinical diagnosis to rule out AD ; this could lead to further diagnostic testing to determine the etiology of dementia, and potentially facilitate avoidance of inappropriate presumptive medication use and/or appropriate use of medications for other types of dementia. The pivotal trials showed a sensitivity of 86% to 93% and a specificity of 86% to 100% compared with the criterion standard of amyloid beta plaque density on postmortem histology. However, the patients in these studies were at the end of life and not representative of the population of patients with suspected AD who present earlier in the course of the disease. Due to the lack of a criterion standard in living patients and limited follow-up, the sensitivity and specificity of amyloid beta PET in patients with suspected AD are unknown. Direct evidence of improved health outcomes with this technology is lacking. A RCT that tested immediate versus delayed reporting of amyloid beta test results for patients with MCI and AD found changes in diagnosis and management, but the effect of these changes on health outcomes such as quality of life, cognitive and behavioral symptoms, and functional outcomes is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a clinical diagnosis of MCI or mild dementia due to AD who are being considered for an U.S. Food and Drug Administration (FDA)-approved amyloid beta plaque-targeting therapy, the evidence includes 2 RCTs and 1 dose-finding and proof of concept phase I trial of aducanumab. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, quality of life, disease-specific survival, and overall survival. ENGAGE (study 301) and EMERGE (study 302) were identical randomized, double-blind, placebo-controlled studies that enrolled patients with early AD. Both trials were terminated early following a prespecified interim analysis for futility. In study 301, there was no treatment benefit observed in either the high- or low-dose arms at week 78. In study 302, a statistically significant difference in change from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) was observed in the high-dose arm (difference vs. placebo, -0.39 [95% CI, -0.69 to -0.09]) but not the low-dose arm at week 78. The observed change of 0.39 was well below the range of 1 to 2 points considered the minimal clinically important difference (MCID). Approval by the FDA was based on reduction in amyloid plaques, which was observed in both trials and at all doses. However, there are no satisfactory data clearly establishing that individual changes in amyloid beta plaque correlate with or predict long-term cognitive and functional changes. In the absence of clinical data demonstrating cognitive and functional effects, it cannot be concluded that the

observed reduction in amyloid will translate into a clinical benefit to patients. Pooled safety data showed that about 35% of patients on aducanumab experienced amyloid-related imaging abnormalities (ARIA); an increased risk of falling was also observed. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health benefit of aducanumab in patients with early AD. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with early AD (MCI or mild dementia due to AD) who are being treated with amyloid beta plaque-targeting therapy and are being evaluated for continuation of therapy, no evidence was identified on the role of subsequent or repeat amyloid beta PET imaging or its correlation with clinical assessment of disease status. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, quality of life, disease-specific survival, and overall survival. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected AD who receive FDG-PET to diagnose AD, the evidence includes systematic reviews of nonrandomized studies. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, and quality of life. The studies included in the reviews were generally of poor quality. There is no standard cutoff for FDG-PET positivity for diagnosing AD, and many studies have not included postmortem confirmation of AD as the reference standard, leading to uncertainty about estimates of performance characteristics. FDG-PET may have high sensitivity and specificity for diagnosing AD, but there is little evidence comparing the performance characteristics of clinical diagnosis using FDG-PET with the clinical diagnosis not using FDG-PET. Therefore, the incremental value of adding FDG-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 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 College of Radiology

The American College of Radiology appropriateness criteria for dementia, revised in 2019, state that amyloid positron emission tomography (PET) and fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) may be appropriate for initial imaging of patients with cognitive decline and suspected Alzheimer disease (AD).[63,]

Society of Nuclear Medicine and Molecular Imaging and Alzheimer's Association

The Appropriate Use Criteria (2013) for amyloid PET were developed jointly by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association.[64,] They recommended that amyloid imaging is appropriate for individuals with all of the following characteristics:

"(i) a cognitive complaint with objectively confirmed impairment; (ii) AD [Alzheimer disease] as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert; and (iii) when knowledge of the presence or absence of AD pathology is expected to increase diagnostic certainty and alter management."

Appropriate candidates include:

1. Patients with unexplained persistent or progressive MCI [mild cognitive impairment]
2. Patients satisfying core clinical criteria for possible AD, but are unusual in the clinical presentation
3. Patients with progressive dementia and atypically early age of onset (eg, 65 years of age or less).

Amyloid imaging is inappropriate in the following situations:

1. "Patients with core clinical criteria for probable AD with typical age of onset

2. To determine dementia severity
3. Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE) ε4
4. Patients with a cognitive complaint that is unconfirmed on clinical examination
5. In lieu of genotyping for suspected autosomal mutation carriers
6. In asymptomatic individuals
7. Nonmedical use (eg, legal, insurance coverage, or employment screening)."

U.S. Preventive Services Task Force Recommendations

In 2020, the USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for cognitive impairment in older adults (I statement).[65,]

Medicare National Coverage

Amyloid Beta Positron Emission Tomography Imaging

The Centers for Medicare & Medicaid Services (CMS; 2013) issued a national coverage determination, through coverage with evidence development, that provides limited coverage for the use of amyloid beta PET imaging in 2 scenarios: (1) clinically difficult differential diagnoses, such as AD versus frontotemporal dementia, when the use of amyloid beta PET imaging may improve health outcomes, and the patient is enrolled in an approved clinical study, and (2) to enrich the Centers for Medicare & Medicaid Services-approved clinical trials of treatments or prevention strategies for AD. The Centers will cover 1 amyloid beta PET scan per patient in clinical studies that meet prespecified criteria.[66,]

Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography

CMS (2004) released a 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." [67,]

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 frontotemporal 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." [68,]

Specific requirements for each indication are clarified in the document.

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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
September 2013	Replace policy	Beta-amyloid imaging with positron emission tomography is investigational.
September 2014	Replace policy	Policy updated with a literature review, adding references 7-9, 14-17, 20- 23, and 26. No changes to the policy statement.
September 2015	Replace policy	Policy updated with literature review through May 19, 2015; references 4-5, 11, 17-18, and 28 added. Policy statements unchanged.
September 2016	Replace policy	Policy updated with literature review through July 24, 2016; references 20-22 added. Policy statement unchanged
December 2017	Replace policy	Policy updated with literature review through July 20, 2017; references 2, 25, and 28-31 added. Policy statement unchanged.
December 2018	Replace policy	Policy updated with literature review through July 9, 2018; references 5, 16-19, 29, and 31 added. Policy statement unchanged.
December 2019	Replace policy	Policy updated with literature review through July 2, 2019; references added. Policy statement unchanged.
December 2020	Replace policy	Policy updated with literature review through August 11, 2020; no references added. Policy statement unchanged.
December 2021	Replace policy	Policy updated with literature review through September 5, 2021; references added. New indications and investigational policy statements added for amyloid beta PET to select patients for amyloid beta targeting therapy and for monitoring treatment. Indication and investigational policy statement on FDG-PET to diagnose Alzheimer disease removed from policy 6.01.06 and added here. Title changed to "Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease" to reflect expanded scope.
December 2022	Replace policy	Policy updated with literature review through August 31, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.