Corporate Medical Policy

Beta Amyloid Imaging With Positron Emission Tomography for Alzheimer's Disease

File Name: beta_amyloid_imaging_with_positron_emission_tomography_for_alzheimers_disease
Origination: 10/2014
Last Review: 5/2023

Description of Procedure or Service

Three radioactive tracers (florbetapir F18, flutemetamol F18, florbetaben F18) that bind to beta amyloid and can be detected in vivo with positron emission tomography (PET) have been developed. This technology is being evaluated to detect beta amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer disease (AD) and/or other causes of cognitive decline.

Background
The diagnosis of AD is divided into 3 categories: possible, probable, and definite AD. A diagnosis of definite AD requires postmortem confirmation of AD pathology, including the presence of extracellular beta amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. There can be a range of beta amyloid plaques and neurofibrillary tanges on histopathology that support a low, intermediate or high probability of AD.

Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. A typical clinical course is defined as an insidious onset, with the initial and most prominent cognitive deficits being either amnestic or nonamnestic, e.g., language, visuospatial, or executive function deficits, and a history of progressively worsening cognition over time. A diagnosis of possible AD dementia is made when the patient meets the core clinical criteria for AD dementia but has an atypical course or an etiologically mixed presentation.

Mild cognitive impairment (MCI) may be diagnosed when there is a change in cognition, but impairment is insufficient for the diagnosis of dementia. Features of MCI are evidence of impairment in one or more cognitive domains and preservation of independence in functional abilities. In some patients, MCI may be a predementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.

Because clinical diagnosis can be difficult, particularly early in the course of disease or with atypical dementia, there has been considerable interest in developing biomarkers for AD. One biomarker that is being evaluated is amyloid plaque density in the brain detected in vivo by PET. However, Aβ is present in individuals without dementia, in patients with mild or subjective cognitive impairment who may or may not progress to dementia, and in patients with other types of dementia, and may be absent in a substantial proportion of patients with clinical features of AD.

PET images biochemical and physiological functions by measuring concentrations of positron-emitting chemicals in the body region of interest. Radiopharmaceuticals used for beta amyloid imaging may be generated in a cyclotron or nuclear generator and introduced into the body by intravenous injection. A number of ^{11}C and ^{18}F-labeled PET radiopharmaceuticals have been investigated for imaging brain beta amyloid.

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Regulatory Status
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."

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."

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Beta amyloid imaging with positron emission tomography (PET) is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Beta amyloid imaging with positron emission tomography (PET) is covered

Not applicable.

When Beta amyloid imaging with positron emission tomography (PET) is not covered

Beta amyloid imaging with positron emission tomography (PET) is considered investigational for all applications.

Policy Guidelines

For individuals who have MCI who receive amyloid beta imaging with PET to predict conversion to AD, 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. 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 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 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 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 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *A9586, Q9982, Q9983*

The PET scan would be reported using 78811 or 78814.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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FDA Pre-Recorded Presentation Slides for the November 6, 2020: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Available at https://www.fda.gov/media/143504/download

Prescribing Label: ADUHELM (aducanumab-avwa) injection, for intravenous use Available at https://www.biogencdn.com/us/aduhelm-pi.pdf

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Policy Implementation/Update Information

10/28/14 New policy developed. Beta amyloid imaging with positron emission tomography (PET) is considered investigational for all applications. Medical Director review 10/2014. (sk)

7/28/15 Specialty Matched Consultant Advisory Panel review 6/24/2015. Reference added. No change to policy statement. (lpr)

12/30/15 Added HCPCS codes C9458 and C9459 to Billing/Coding section for effective date 1/1/2016. (lpr)

7/26/16 Codes Q9982, Q9983 added to Billing/Coding section. Specialty Matched Consultant Advisory Panel review 6/29/2016. No change to policy statement. (an)

6/30/17 Updated Policy Guidelines. Added reference. Specialty Matched Consultant Advisory Panel review 5/26/2017. No change to policy statement. (an)

6/29/18 Updated Description and Policy Guidelines sections. Added reference. Codes C9458 and C9459 deleted from Billing/Coding section. Specialty Matched Consultant Advisory Panel review 5/23/2017. No change to policy statement. (an)

6/11/19 Updated Policy Guidelines. Added reference. Specialty Matched Consultant Advisory Panel review 5/15/2019. No change to policy statement. (an)

6/9/20 References updated. Specialty Matched Consultant Advisory Panel review 5/20/2020. No change to policy statement. (eel)

6/1/21 References updated. Specialty Matched Consultant Advisory Panel review 5/2021. Medical Director review 5/2021. No change to policy statement. (bb)

5/31/22 References updated. Specialty Matched Consultant Advisory Panel review 5/2022. Medical Director review 5/2022. Related policy removed. No change to policy statement. (tt)

5/30/23 Regulatory status, policy guidelines, and references updated. Specialty Matched Consultant Advisory Panel review 5/2023. Medical Director review 5/2023. No change to policy statement. (tt)

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