

## 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 CAP Review:** 5/2019  
**Next CAP Review:** 5/2020  
**Last Review:** 5/2019

#### 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 tangles 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 amnesic or nonamnesic, 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 1 or more cognitive domains and preservation of independence in functional abilities. In some patients, MCI may be a prodementia 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, 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, A $\beta$  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

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

intravenous injection. A number of <sup>11</sup>C and <sup>18</sup>F-labeled PET radiopharmaceuticals have been investigated for imaging brain beta amyloid.

## Regulatory Status

In 2012, FDA approved florbetapir F18 (Amyvid™; Avid Radiopharmaceuticals [a subsidiary of Eli Lilly], Philadelphia, PA) as a radioactive agent for visualizing amyloid plaque in the brain. The FDA document prepared for the advisory committee meeting indicated that although florbetapir may detect pathology, there could be no claim of disease detection, because beta amyloid aggregates can be found in cognitively normal elderly patients, as well as patients with AD.

In October 2013 and March 2014, FDA approved 2 other radioactive diagnostic imaging agents for detecting beta-amyloid plaque, flutemetamol F18 (Vizamyl™; GE Healthcare) and florbetaben F18 (Neuraceq™; Piramal Life Sciences, Matran, Switzerland), respectively.

Amyvid™, Vizamyl™, and Neuraceq™ are indicated “for PET imaging of the brain to estimate beta amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer disease and other causes of cognitive decline.” Prescribing information for all 3 agents states:

- The objective of beta amyloid image interpretation “is to estimate beta-amyloid neuritic plaque density in brain gray matter, not to make a clinical diagnosis.”
- A positive beta amyloid scan “does not establish the diagnosis of AD or other cognitive disorder.”
- A negative beta amyloid 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.”

## Related Policy

Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography

***\*\*\*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.

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

## 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 A $\beta$  imaging with PET, the evidence includes studies on diagnostic accuracy and an RCT that evaluated changes in diagnosis and changes in management. Relevant outcomes are test performance measures, symptoms, and functional outcomes. Studies evaluating the diagnostic accuracy of A $\beta$  PET in patients with MCI, using conversion to probable AD as a reference standard, report that patients with a positive A $\beta$  PET scan at baseline have an increased risk of conversion to probable AD at 3 years. The negative predictive value of A $\beta$  PET in these studies ranged from 77% to 95%. There are currently no disease-modifying drugs, and direct evidence of improved health outcomes with this technology is lacking. An RCT tested immediate vs delayed reporting of A $\beta$  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 the effects of the technology on health outcomes.

For individuals who have dementia who receive A $\beta$  imaging with PET, the evidence includes studies on diagnostic accuracy and an RCT that evaluated changes in diagnosis and in management. Relevant outcomes are test performance measures, symptoms, and functional outcomes. One possible use of A $\beta$  testing is as an adjunct to clinical diagnosis to rule out AD, which could lead to further diagnostic testing to determine the etiology of dementia and avoidance of unnecessary medications. The pivotal trials showed a sensitivity of 86% to 93% and a specificity of 86% to 100% compared with the criterion standard of A $\beta$  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 A $\beta$  PET in patients with suspected AD are unknown. Direct evidence of improved health outcomes with this technology is lacking. An RCT that tested immediate vs delayed reporting of A $\beta$  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, symptoms, and functional outcomes is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

## 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](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: A9586, A9599, 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.

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

## Scientific Background and Reference Sources

---

Hyman BT, Phelps CH, Beach TG et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement* 2012; 8(1):1-13. Available online at: [http://www.alzheimersanddementia.com/article/S1552-5260\(11\)02980-3/fulltext](http://www.alzheimersanddementia.com/article/S1552-5260(11)02980-3/fulltext) . Last accessed October 2014.

Albert MS, DeKosky ST, Dickson D et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7(3):270-9. Available online at: [http://www.alz.org/documents\\_custom/diagnostic\\_recommendations\\_mci\\_due\\_to\\_alz\\_proof.pdf](http://www.alz.org/documents_custom/diagnostic_recommendations_mci_due_to_alz_proof.pdf) Last accessed October 2014.

U.S. Food and Drug Administration. FDA Advisory Committee briefing document: Peripheral and central nervous system drugs advisory committee. 2011. Available online at: [http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240265.pdf?utm\\_campaign=Google2&utm\\_source=fdaSearch&utm\\_medium=website&utm\\_term=amyvid&utm\\_content=5](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240265.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=amyvid&utm_content=5) . Last accessed October 2014.

Eli Lilly and Company. Amyvid™ (florbetapir F18 injection) for intravenous use prescribing information, December 2013. Available online at: <http://www.amyvid.com/Pages/index.aspx> . Last accessed October 2014.

Piramal Imaging. Neuraceq (florbetaben F 18 injection) for intravenous use prescribing information, April 2014. Available online at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/204677s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204677s000lbl.pdf) . Last accessed October 2014.

GE Healthcare. Vizamy1™ (flutemetamol F18) injection prescribing information, October 2013. Available online at: [http://www3.gehealthcare.com/en/Products/Categories/Nuclear\\_Imaging\\_Agents/Vizamy1](http://www3.gehealthcare.com/en/Products/Categories/Nuclear_Imaging_Agents/Vizamy1) . Last accessed October 2014.

Alzheimer's Association. Alzheimer's Association statement on FDA approval of florbetapir (Amyvid). 2012. Available online at: [http://www.alz.org/documents\\_custom/amyvid.pdf](http://www.alz.org/documents_custom/amyvid.pdf). Last accessed October 2014.

BCBSA Medical Policy Reference Manual [Electronic Version]. 6.01.55, 6/12/14

BCBSA Medical Policy Reference Manual [Electronic Version]. 6.01.55, 6/11/15

Specialty Matched Consultant Advisory Panel review- 6/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 6.01.55, 9/8/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 6.01.55, 9/14/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 6.01.55, 9/13/2018

## Policy Implementation/Update Information

---

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

- 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)

---

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.