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

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. 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 1 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, 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. However, due to their short half-life (20 minutes), $^{11}$C radiotracers are not convenient for commercialization. Several $^{18}$F beta amyloid radiotracers are currently in phase 2 and 3 clinical trials.
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**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 Policies and Guidelines**
Biochemical Markers of Alzheimer’s Disease
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.

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

For individuals who have suspected Alzheimer disease (AD) who receive β-amyloid (Aβ) imaging with positron emission tomography (PET), the evidence includes pivotal studies for 3 agents. Relevant outcomes are test accuracy, other test performance measures, functional outcomes, and medication use. Literature on the use of Aβ PET to aid in the diagnosis of patients with suspected AD is limited. A pivotal phase 3 trial with florbetapir, although to be commended for its use of the criterion standard (histopathology), had a number of limitations including small sample size, use of a majority rating of 3 physicians, and very few patients in the mildly impaired category. The pivotal florbetaben and flutemetamol studies did not include patients with mild cognitive impairment (MCI). The sensitivity and specificity of Aβ imaging with PET have not yet been adequately determined in an appropriate population, including a larger number of patients with MCI. In addition, direct or indirect evidence of improved health outcomes with this technology is lacking. Aβ imaging with PET is not likely to help confirm AD in patients who present with cognitive impairment. It may have a role in ruling out AD in patients with MCI, but the diagnostic accuracy of testing in patients with MCI is too uncertain to determine whether testing is likely to impact management and/or lead to improved outcomes. 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 website at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: A9586, A9599, C9458, C9459, 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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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)


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
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and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.