Policy Statement

Beta-amyloid imaging with positron emission tomography (PET) is considered investigational.

Policy Guidelines

There are HCPCS codes specific to the current U.S. Food and Drug Administration (FDA)-approved radiopharmaceuticals for this imaging:

- **A9586**: Florbetapir F18, diagnostic, per study dose, up to 10 millicuries
- **Q9982**: Flutemetamol F18, diagnostic, per study dose, up to 5 millicuries
- **Q9983**: Florbetaben F18, diagnostic, per study dose, up to 8.1 millicuries

The positron emission tomography (PET) scan would be reported using the CPT codes for PET or PET with computed tomography scanning:

- **78811**: Positron emission tomography (PET) imaging; limited area (e.g., chest, head/neck)
- **78814**: Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; limited area (e.g., chest, head/neck)

Description

Three radioactive tracers (florbetapir fluorine 18, florbetaben fluorine 18, flutemetamol fluorine 18) that bind to β-amyloid (Aβ) and can be detected in vivo with positron emission tomography (PET) have been developed. This technology is being evaluated to detect Aβ neuritic plaque density in adults with cognitive impairment who are being evaluated for Alzheimer disease (AD).

Related Policies

- Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease
- Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography
- Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 2012, florbetapir F18 (Amyvid™; Avid Radiopharmaceuticals [a subsidiary of Eli Lilly], Philadelphia, PA) was approved by the U.S. Food and Drug Administration (FDA) through the...
premarket approval process 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 Aβ aggregates can be found in cognitively normal elderly patients as well as patients with AD.8

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

Amyvid™, Vizamyl™, and Neuraceq™ are indicated “for PET imaging of the brain to estimate Aβ neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer disease (AD) and other causes of cognitive decline.”9-11 Prescribing information for all 3 agents states:

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

### Rationale

#### Background

##### Alzheimer Disease

#### Diagnosis

The diagnosis of Alzheimer disease (AD) is divided into 3 categories: possible, probable, and definite AD.1 A diagnosis of possible AD dementia is made when the patient meets the core clinical criteria for AD dementia but has a typical clinical course or an etiologically mixed presentation.

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. In a study of the clinical diagnosis of possible or probable AD at national AD centers, sensitivity was shown to range from 83% to 87%, with specificity ranging from 54% to 44%, depending on the criteria used to establish AD at autopsy.2

A diagnosis of definite AD requires postmortem confirmation of AD pathology, including the presence of extracellular β-amyloid (Aβ) plaques and intraneuronal neurofibrillary tangles in the cerebral cortex.3 The range of Aβ plaques and neurofibrillary tangles on histopathology may be described by the CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) neuritic plaque density score, Thal stage, and Braak stage for neurofibrillary tangles. Histopathologic diagnosis must also take into account the age of the individual, because neuritic plaques and tangles increase with age in cognitively normal elderly.

Mild cognitive impairment (MCI) may be diagnosed when there is a change in cognition, but impairment is insufficient for the diagnosis of dementia.4 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
Because clinical diagnosis can be difficult, particularly early in the course of the disease, there has been considerable interest in developing biomarkers for AD (see Blue Shield of California Medical Policy: Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease). One biomarker being evaluated is Aβ plaque density in the brain detected in vivo by positron emission tomography (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; conversely, it may be absent in a substantial proportion of patients with clinical features of AD.5,6

PET images biochemical and physiologic functions by measuring concentrations of positron-emitting chemicals in the body region of interest. Radiopharmaceuticals used for Aβ imaging may be generated in a cyclotron or nuclear generator and introduced into the body by intravenous injection. A number of carbon 11- and fluorine 18-labeled PET radiopharmaceuticals have been investigated for imaging brain Aβ.7

Literature Review
Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (including test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, positive and negative predictive values) in relevant populations of patients; and (3) clinical utility (i.e., demonstration that the diagnostic information can be used to improve patient outcomes).

β-Amyloid Imaging with Positron Emission Tomography for Suspected Alzheimer Disease
Clinical Context and Test Purpose
The purpose of β-amyloid (Aβ) imaging with positron emission tomography (PET) is to determine the Aβ burden in patients who have suspected Alzheimer disease (AD) to provide a differential diagnosis and guide appropriate treatment.

The following PICOTS were used to select literature to inform this review.

Patients
The population of interest includes patients with suspected AD.

Interventions
The intervention of interest is Aβ imaging using a commercially available PET tracer (florbetapir fluorine 18, florbetaben fluorine 18, or flutemetamol fluorine 18).

Comparators
The criterion standard for the diagnosis of AD is postmortem neuropathologic examination. In the absence of comparisons with the criterion standard, long-term clinical follow-up may be used as a surrogate end point to evaluate the diagnostic performance of Aβ imaging with PET.

Outcomes
The current clinical purpose of testing for Aβ plaque density would be to improve the diagnostic accuracy of AD. Although direct evidence of an improvement in health outcomes is the preferred outcome, in the absence of direct evidence, a chain of evidence may be built. In general, a chain of evidence of a health benefit or clinical utility of testing requires a demonstration that:

- incremental improvements in diagnostic or prognostic accuracy over current practice occur, and
- incremental improvements lead to improved health outcomes (e.g., by informing clinical management decisions), and
• these outcomes may be obtained (i.e., are generalizable) outside of the investigational setting.

**Timing**

Diagnostic accuracy can only be confirmed at autopsy or after several years to monitor progression (or lack of progression) of disease.

**Setting**

The setting is a dementia specialist practice for patients undergoing evaluation for AD or other causes of dementia.

**Technical Reliability**

Evidence on technical reliability of Aβ imaging for AD should demonstrate that the test measures what it is intended to measure (i.e., Aβ plaque). The best evidence on this would be a direct comparison with a criterion standard test (histopathologic examination) for measuring amyloid plaque. Other important measures of technical performance are the reliability of testing, including both test-retest reliability and interobserver reliability in reading test results.

**Florbetapir**

Data on the technical reliability of the test were included in a florbetapir pivotal study published in 2011.8,12 This study was a phase 3 multicenter trial with 2 separate cohorts. These cohorts were an autopsy cohort and a young, cognitively intact cohort. The autopsy cohort was drawn from 152 patients who had a projected life expectancy of 6 months or less. Thirty-five patients died and were autopsied within 12 months of PET imaging; 29 were included in the primary efficacy analysis. This cohort comprised 9 (31%) patients who were not cognitively impaired, 2 (7%) who were mildly impaired, 13 (45%) with a clinical diagnosis of AD, and 5 (17%) with a clinical diagnosis of non-AD dementia.

All patients had a direct measurement of amyloid burden by histopathologic examination, and 52% met pathologic criteria for AD. A significant correlation (0.78) was found between amyloid burden in the brain measured by Amyvid and histopathology; however, there was not an exact match between the 2 measures. The correlation between quantitative whole-brain florbetapir image scores and postmortem silver stain was 0.71. In a specificity cohort to evaluate false positives, the primary efficacy end point was the exclusion of amyloid on PET scans of 47 young controls who were negative for the apolipoprotein E ε4 (APOE4) allele, randomly interspersed with PET scans of 40 patients in the autopsy cohort. The study achieved a specificity of 100% in this cohort, although it was noted that the young controls were outside of the intended use population.

Reproducibility of the readings was assessed using 3 trained readers blinded to clinical information. The study used a binary scale (positive or negative for amyloid), and sensitivity ranged from 55% to 90% for the 3 readers, and in 24% to 45% of the images (depending on the sample), at least 1 reader would have had a different interpretation of amyloid status from the other readers.8 Subsequent reanalysis for publication used the majority rating of 3 nuclear medicine physicians as the primary outcome variable, resulting in 96% agreement between PET images using fluorine 18 (florbetapir) and histopathologic results in the 29 patients in the primary analysis cohort.12

In 2012, Clark et al published an extension of their pivotal study submitted to the U.S. Food and Drug Administration for the marketing application of florbetapir.13 This study reported on 59 participants with cognitive status ranging from normal to advanced dementia. Twelve participants had no cognitive impairment, 5 had MCI not meeting the criteria for dementia, 29 had AD, and 13 had other forms of dementia. All participants had a direct measurement of amyloid burden by histopathologic examination, and images were interpreted by 3 readers using semiquantitative visual analysis on a scale from 0 to 4; median semiquantitative rating was used. A significant correlation of 0.76 and 0.79 was found between amyloid burden in the brain
measured by florbetapir and the criterion standard of histopathology in patients who had an autopsy performed within 2 years and 12 months of imaging, respectively. This report added additional participants to those reported in the 2011 study (described above).

Siderowf et al (2014) compared patterns of amyloid deposition by florbetapir PET imaging in 31 patients with probable AD (n=10), probable dementia with Lewy bodies (n=11), or probable Parkinson disease (n=5), and 5 healthy controls. Diagnoses were made by research criteria. PET images were read by 5 readers blinded to clinical data; the majority interpretation was used for analysis. Interrater agreement was high (κ=0.88; 95% confidence interval [CI], 0.77 to 0.99). Differences in the standardized uptake value ratio (SUVR) between healthy controls and patients with AD, and between patients with Parkinson disease and patients with AD, were statistically significant. Differences in SUVR between patients with Lewy body dementia and patients with AD were statistically significant in only 2 of 6 brain regions imaged. However, statistical analyses were not corrected for multiple comparisons. This study also had a small sample size and lacked histopathologic confirmation of probable dementia diagnoses.

Florbetaben
Information about the technical reliability of florbetaben is provided in the prescribing information. Reliability and reproducibility of image interpretation were evaluated using 5 new readers and images from 273 patients and 188 healthy controls enrolled in previous studies. Patients had AD (67%), MCI (19%), other dementias (13%), or Parkinson disease (2%). The median age of all 461 enrollees was 72 years (range, 22-98 years); 43% were female; 78% were white. Readers were trained by electronic media rather than in-person. Interreader agreement was high across scans from all patients (κ=0.80; 95% CI, 0.77 to 0.83) and for scans from 54 patients who underwent postmortem autopsy (κ=0.75; 95% CI, 0.67 to 0.83). Intrareader reproducibility for 46 images ranged from 91% to 98% across the 5 readers.

Flutemetamol
Another study that used autopsy as the criterion standard for diagnosis was the pivotal cohort study of flutemetamol. This study assessed diagnostic accuracy (see Table 1) and reproducibility (both intra- and interreader) of flutemetamol PET imaging. The criterion standard was postmortem brain amyloid density: 43 (63%) were positive on histopathology review, and 25 (37%) were negative. Interreader reproducibility was a κ of 0.80 (95% CI, 0.79 to 0.86). Intrareader reproducibility on 29 duplicate images was reported to be high.

Fluorine 18–Labeled Aβ Tracers
In 2013, Vandenberghe et al summarized published studies on test-retest variability and interrater reliability of all 3 tracers. As shown in

Table 1, variability in repeat testing was low for each agent, and interrater reliability (κ) varied from 0.6 to 0.96. Because values listed in

Table 1 were derived from heterogeneous studies, cross-tracer comparisons are indirect.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Florbetapir</th>
<th>Florbetaben</th>
<th>Flutemetamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) test-retest variability of SUVR, %</td>
<td>2.4 (1.4)</td>
<td>6.2 (range, 0.6-12.2)</td>
<td>1.5 (0.7)</td>
</tr>
<tr>
<td>Interrater consistency of binary readings, κ</td>
<td>0.58-0.76</td>
<td>0.60</td>
<td>0.96</td>
</tr>
</tbody>
</table>

PET: Positron Emission Tomography; SUVR: Standardized Uptake Value Ratio using cerebellum as reference region.

a In patients with Alzheimer dementia scanned within 1 month from clinical diagnosis.
b Positive or negative.

Use of SUVR has been shown to decrease interreader variability of florbetapir PET scan interpretation (κ=0.92) compared with qualitatively read studies (κ=0.69). However, as Minoshima (2015) noted in an accompanying editorial, if cases have differing impressions between qualitative interpretation and quantitative assessment, it is not known which is more accurate.
Section Summary: Technical Reliability
Evidence on technical reliability is mainly from pivotal studies. A strength of the florbetapir pivotal study and the phase 3 studies of florbetaben and flutemetamol was the comparison of imaging with the criterion standard of postmortem histopathology. Limitations of the florbetapir study included small sample size, a majority rating for assessing diagnostic accuracy, and the inclusion of only 2 patients in the MCI category, which is the population for whom the test is most likely to be used. Similarly, the florbetaben and flutemetamol studies did not include patients with MCI. Evidence from these studies has indicated that agreement between histopathology and Aβ testing by PET is good but not perfect. There is evidence for interobserver variability in reading the test; using a majority of 2 of 3 readers leads to a high agreement with histopathology. A summary review and prescribing information have indicated that test-retest variability is low while interrater reliability is sufficient.

Clinical Validity
The lack of a criterion standard for the diagnosis of AD for use in living patients is a barrier to high-quality research. The highest quality studies of diagnostic accuracy are those that use a pathologic examination of brain tissue in deceased patients and include a population of patients with AD, MCI, other neurologic disorders, and patients without neurologic disease. The main limitation of these studies is the patient population, which may not be representative of the population for which the test is intended.

Florbetapir
The first study that used the criterion standard postmortem histopathology as the reference standard was the 2011 pivotal study by Clark et al that reported on the diagnostic accuracy of florbetapir.13,12 The pivotal study used a majority consensus of 3 independent reviewers as the final test reading. The extension study used majority consensus of 5 independent reviewers rating the images on a binary scale of amyloid-positive or -negative as the final test reading. According to clinical criteria, there were 12 individuals with no cognitive impairment, 5 with MCI, 29 with AD, and 13 with other forms of dementia. Sensitivity and specificity are shown in Table 2. In 46 participants with a scan-to-autopsy time of less than 12 months, accuracy was 98% (87%-100%). For those with a scan-to-autopsy time of less than 2 years, accuracy was 95% (85%-99%).

A 2011 industry-funded multicenter study by Fleisher et al pooled data from 4 phase 1 and 2 trials of florbetapir PET imaging for a total of 210 participants, including 68 patients with probable AD, 60 patients with MCI; and 82 older unimpaired controls.19 Although there were significant differences in mean SUVRs across groups, there was considerable overlap in the range of values. The percentages of patients meeting threshold levels of amyloid with clinical AD, MCI, and cognitively healthy controls were 80.9%, 40.0%, and 20.7%, respectively. The percentage of patients with any identifiable florbetapir signal was 85.3%, 46.6%, and 28.1%, respectively. Among healthy controls, the percentage of patients with any florbetapir positivity increased linearly by age, ranging from 11.8% for patients 55 to 60 years of age to 41.7% for patients 81 years of age or older. APOE4 carriers in the control group had approximately twice the percentage of florbetapir positivity as noncarriers, although this comparison was not statistically significant.

Other studies have used the clinical diagnosis of AD as the criterion standard, enrolling patients similar to those seen in clinical care. The most relevant design for clinical use conducts imaging in patients with MCI or possible AD and follows the patients to determine whether they convert to probable AD or confirmed AD on autopsy. In a follow-up to an earlier study,20 Doraiswamy et al (2014) compared cognitive decline in 47 patients with MCI who were Aβ-positive or Aβ-negative by florbetapir PET imaging.21 Over 36 months of follow-up, 6 (35%) of 17 Aβ-positive patients and 3 (10%) of 30 Aβ-negative patients advanced to a diagnosis of AD or clinically significant worsening (defined as a 4-point decline on the 11-item Alzheimer Disease Assessment Scale, \( p=0.054 \)). Sensitivity, specificity, positive predictive value, and negative predictive value for these outcomes combined were 67%, 71%, 35%, and 90%, respectively.
Florbetaben
In 2015, Sabri et al published the phase 3, histopathologic study of florbetaben PET for detecting neuritic Aβ plaque.22 Patients with clinical diagnoses of AD, dementia with Lewy bodies, or other dementias; patients without dementia (primarily with oncologic disorders); and a cohort of young (age, 22-38 years), cognitively normal healthy volunteers considered highly likely to be Aβ-negative (n=11) were included. The optimal thresholds for sensitivity and specificity for detecting Aβ were determined by quantitative SUVR receiver operating characteristic curve analysis. At the time of data analysis, 74 (36%) of 207 patients had died. At autopsy, Aβ was present in 44 (77%) of 57 patients diagnosed clinically with AD, 1 (33%) of 3 patients with Lewy body dementia, 1 (17%) of 6 patients with other dementias, and 1 (13%) of 8 patients without dementia. Forty-six of 47 neuritic Aβ-positive cases were read as florbetaben-PET positive, and 24 of 27 neuritic Aβ-negative cases were read as PET negative. Interrater agreement was high (κ=0.90; 95% CI, 0.81 to 0.98). Using an optimized quantitative SUVR threshold, sensitivity was 89%, and specificity was 92% (see Table 2).

Table 2. Trial Results Using Histopathology of Plaque as the Reference Standard

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>n</th>
<th>Clinical Diagnosis</th>
<th>Interval From Imaging</th>
<th>Readers</th>
<th>Sensitivity, % (95% CI or Range)</th>
<th>Specificity, % (95% CI or Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark et al (2011)florbetapir</td>
<td>35</td>
<td>End-of-life cohort</td>
<td>≤12 mo</td>
<td>Majority of 3 readers</td>
<td>93 (68-100)</td>
<td>100 (76.8-100)</td>
</tr>
<tr>
<td>Clark et al (2012)florbetapir</td>
<td>59</td>
<td>End-of-life cohort (addition of 24 patients to Clark et al, 2011)</td>
<td>≤ 2 y</td>
<td>Majority of 5 readers</td>
<td>92 (78-98)</td>
<td>100 (80-100)</td>
</tr>
<tr>
<td>Sabri et al (2015)florbetaben</td>
<td>74</td>
<td>AD/non-AD dementia/dementia with Lewy body/no evidence of dementia</td>
<td>329 d[^a]</td>
<td>3</td>
<td>89 (81 to 98)</td>
<td>92 (82 to 100)</td>
</tr>
</tbody>
</table>
| Curtis et al (2015)flutemetamol | 68  | • 30 probable AD  
• 17 non-AD impairment 
• 21 not affected                             | ≤13 mo                | 5                         | 88\[^b\] (81-93)                | 88\[^b\] (44 to 92)             |
| Salloway et al (2017)flutemetamol | 106 | End-of-life cohort (addition of 38 patients to Curtis et al, 2015)            | 7.5 mo\[^a\] (range, 0-28) | Majority of 5 readers    | 86 to 92\[^c\]                   | 86 to 100\[^c\]                |

AD: Alzheimer Disease; CI: Confidence Interval.
\[^a\] Mean.
\[^b\] Median.
\[^c\] Varies by reference standard.

Ong et al (2013) compared florbetaben PET-SUVR in 45 patients with MCI and a separate cohort of 15 patients with probable AD.25 Mean (SD) SUVR across 6 brain regions imaged was statistically higher in patients with AD (1.96 [0.27]) compared with patients who had MCI (1.54 [0.27]; p<0.05). All patients with AD (100%) and 24 (53%) patients with MCI had high Aβ, defined by a cutoff value for mean SUVR of 1.45 or greater. In 2- and 4-year follow-ups of the MCI cohort (n=45), Ong et al (2015) reported that 18 (75%) of 24 patients with baseline Aβ-positive PET scans (by semiquantitative SUVR interpretation) progressed to AD within 2 years compared with 2 (10%) of 21 patients with baseline Aβ-negative PET scans.26 Positive predictive value and negative predictive value for progression to AD at 2 years were approximately 76% and 91% to 95%, respectively, depending on method of image interpretation (semiquantitative vs visual read). At 4 years, 21 (88%) of 24 patients with baseline Aβ-positive PET scans had probable AD, and 5 (24%) of 21 patients with baseline Aβ-negative PET scans had developed a non-AD form of dementia. As in the original study, histopathologic confirmation of AD diagnoses was lacking.
**Flutemetamol**

In 2015, Curtis et al published an international, phase 3, histopathologic, pivotal study of flutemetamol-PET for detecting neuritic Aβ plaque (N=203). The study included patients with AD, other dementia, unspecified memory loss, or no cognitive impairment who were 55 years or older and terminally ill with a life expectancy of 1 year or less. PET images were read by four nuclear medicine physicians and one radiologist using a majority-read approach. Of 69 patients who died during the study (mean age, 81 years), 43 (63%) brains were Aβ-positive, and 25 (37%) were Aβ-negative by histopathology (1 brain was not evaluated). Flutemetamol-PET imaging was performed a mean of 3.5 months (range, 0-13 months) before death. The median sensitivity of flutemetamol PET imaging for Aβ was 88%, and median specificity was 88% (see Table 2). Intermater and intrarater agreement was high (Fleiss κ=0.72, Cohen κ range, 0.60-1.00 across raters, respectively).

Buckley et al (2017) reported on an industry-sponsored study assessing the efficacy of an electronic training program for inexperienced readers. Following training, 5 readers were tested in a blinded manner with a randomized sample of 305 images obtained from previous studies. The sample scans included patients with MCI, normal pressure hydrocephalus, probable AD, and young and older healthy controls. For the population of 68 patients who had died and had histopathology results (see Curtis et al, above), the median sensitivity for the electronically trained readers was 93% (95% CI, 86% to 93%) and specificity was 84% (95% CI, 60% to 92%). The authors reported that the false positives (up to 16%) were related to a low level of neuritic plaque but a substantial number of diffuse plaques, while the false negatives (up to 9%) were related to cortical atrophy and/or borderline neuritic plaque. In a sample of images from patients with MCI, intrarater reproducibility was 100%.

In 2017, Salloway et al reported on the diagnostic accuracy of flutemetamol in 106 end-of-life patients who underwent postmortem histopathology for Aβ plaque load (see Table 2). This report was an extension of the 2015 study by Curtis (described above), with an additional 38 individuals from the cohort who had died and undergone an autopsy. All scans (n=106) were evaluated by 5 independent and blinded readers who had not previously read the images. Imaging interpretations (dichotomous Aβ positive or negative) were compared with 3 different scales for the histologic rating of neuritic plaques (Consortium to Establish a Registry for Alzheimer’s Disease [CERAD] original, CERAD modified, and the 2012 National Institute on Aging-Alzheimer’s Association guidelines for Thal phasing). Sensitivity and specificity varied by histopathologic scale used. Sensitivity was highest (91.9%) when the reference standard was conducted with the original CERAD, while specificity was highest (100%) when the reference standard was Thal phasing. Thal phasing includes both neuritic and diffuse plaques; it was proposed by Buckley et al (above) that the false positives in their study were due to diffuse plaques. Agreement among all 5 readers was 84.9% (Fleiss κ=0.82) while intrarater repeatability was 100%.

**Section Summary: Clinical Validity**

The evidence on PET ligands for visualization of Aβ plaque burden in vivo includes pivotal trials for 3 different tracers. These trials have shown sensitivity around 90% and specificity up to 100% when dichotomous image interpretation is compared with the criterion standard (histopathology of Aβ plaque). The participants in these studies were at the end of life and included patients with probable AD and other causes of dementia, as well as with patients without dementia who were dying of other causes. One potential use is to rule-out AD in patients with atypical presentation of dementia. It is unclear how many, if any, of the included patients were consistent with the intended use. The high specificity indicates that patients with positive scans have a high likelihood of clinically significant Aβ plaque at the time of autopsy. However, Aβ plaque is only one of several markers of AD on histopathology and cannot by itself be considered a diagnosis of AD. Also, it cannot be determined from these studies whether Aβ imaging would be able to identify patients with MCI who are either likely or unlikely to progress to AD. Additional study with long-term follow-up is needed to determine whether Aβ PET imaging could improve the diagnostic distinction between AD and non-AD dementia.
Clinical Utility
Possible uses of Aβ testing as an adjunct to clinical diagnosis could include confirming the
diagnosis of AD to begin medications at an earlier stage, or ruling out AD, which could lead to
further diagnostic testing to determine the etiology of dementia and/or avoidance of anti-
Alzheimer medications that would be unnecessary. Several multicenter studies have reported on
changes in diagnosis and patient management following Aβ PET imaging.²⁸-³⁰ However, no trials
have been identified that reported whether the changes in management improved patient
health outcomes. Thus, there is no direct evidence for clinical utility.

For example, in 2016, Boccardi et al reported on results from the prospective, multicenter open-
label Incremental Diagnostic Value of Amyloid PET with [18F]-Florbetapir (INDIA-FBP) study.²⁹ The
study included 228 consecutive adults with cognitive impairment who were evaluated by a
dementia specialist for AD or other causes of cognitive decline. Patients underwent a routine
diagnostic workup including ancillary tests. Before Aβ imaging, the specialists reported their
confidence that the findings were consistent with an AD diagnosis. About 65% of patients with a
prescan diagnosis of AD, and about 50% of patients with a prescan diagnosis of non-AD, had a
positive scan. Following imaging, there was an increase in diagnostic confidence and change in
medications, particularly for patients diagnosed with non-AD who had a negative scan. Of 137
patients with a positive scan, 123 (89.8%) received a final diagnosis of AD, and 79 (86.8%) of 91
patients with a negative scan received a final diagnosis of non-AD. It cannot be determined
from this study whether the revised diagnoses were correct, and without longer follow-up the
effect of the management changes on health outcomes is uncertain.

A 2017 prospective study by Zwan et al identified changes in diagnosis and management
following Aβ imaging in patients who were evaluated for suspected early-onset AD at tertiary
memory clinics.³⁰ Flutemetamol scans were positive in 133 (63%) of 211 patients, and imaging led
to a change in diagnosis in 41 (19%) patients. The authors proposed that Aβ PET imaging might
be particularly helpful in this younger population, where Aβ burden will not be confounded by
age-related accumulation of Aβ plaque. This ongoing study will evaluate the diagnostic
accuracy of Aβ imaging after a 2-year clinical follow-up period.

Section Summary: Clinical Utility
Direct evidence on clinical utility (i.e., that health outcomes are improved by testing) is lacking.
There are no studies that report on clinical outcomes after testing.

A chain of evidence of a health benefit or clinical utility of testing requires demonstration of
several elements: that incremental improvements in diagnostic or prognostic accuracy over
current practice occur; that incremental improvements lead to improved health outcomes
(e.g., by informing clinical management decisions); and that these outcomes may be obtained
(i.e., are generalizable) outside of the investigational setting. Several studies have reported a
change in diagnosis, increased confidence in diagnosis, and change in management after
testing. However, there is currently no evidence that Aβ imaging leads to an improvement in the
differential diagnosis of AD and non-AD dementia over current clinical practice.

Diagnostic accuracy in patients with MCI is uncertain. Because the sensitivity and specificity of
Aβ testing have not yet been established in patients with MCI, it is not possible to determine a
chain of evidence that would indicate improvement in health outcomes. Longer term follow-up
in a relevant patient population is needed to determine whether PET imaging is sufficient to rule
in or rule out AD in patients with MCI.

Summary of Evidence
For individuals who have suspected AD who receive Aβ imaging with PET, the evidence includes
pivotal studies for 3 agents. Relevant outcomes are test accuracy, other test performance
measures, symptoms, and functional outcomes. The pivotal trials showed moderately high
sensitivity and specificity compared with histopathology of Aβ plaque in patients with possible or
probable AD, and several studies have reported a change in diagnosis and a change in management after testing. However, histopathologic diagnosis of AD depends on several biomarkers, and there is currently no evidence that Aβ imaging leads to an improvement in the differential diagnosis of AD and non-AD dementias over current clinical practice. The pivotal phase 3 trial with florbetapir 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 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. Also, 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.

Supplemental Information
Practice Guidelines and Position Statements

Society of Nuclear Medicine and Molecular Imaging and Alzheimer's Association
The 2013 Appropriate Use Criteria for amyloid positron emission tomography (PET) were developed jointly by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association. 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 (e.g. 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 a polypolypeptide 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 (e.g., legal, insurance coverage, or employment screening)”

National Institute on Aging and Alzheimer Association’s
The 2011 guidelines from the National Institute on Aging and the Alzheimer Association’s on the diagnosis of MCI and dementia due to AD recommended the use of biomarkers, including β-amyloid (Aβ) imaging with PET, only in research settings. Reasons for this recommendation included the need for more research to ensure that criteria for using biomarkers have been appropriately designed; limited standardization of biomarkers from one locale to another; and access to biomarkers may be limited in community settings.

U.S. Preventive Services Task Force Recommendations
Not applicable.
Medicare National Coverage
In 2013, the Centers for Medicare & Medicaid Services (CMS) issued a national coverage determination, through coverage with evidence development, that provides limited coverage for the use of Aβ PET imaging in 2 scenarios: (1) clinically difficult differential diagnoses, such as AD vs frontotemporal dementia, when the use of Aβ PET imaging may improve health outcomes, and the patient is enrolled in an approved clinical study, and (2) to enrich CMS-approved clinical trials of treatments or prevention strategies for AD. CMS will cover 1 Aβ PET scan per patient in clinical studies that meet prespecified criteria.32

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01886820a</td>
<td>A Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of [18F]NAV4694 PET for Detection of Cerebral Beta-Amyloid When Compared With Postmortem Histopathology</td>
<td>290</td>
<td>Dec 2017</td>
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<tr>
<td>NCT01518374a</td>
<td>Clinical Evaluation of Florbetapir F 18 (18F-AV-45)</td>
<td>1800</td>
<td>Dec 2017</td>
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<tr>
<td>NCT02420756</td>
<td>Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study: A Coverage With Evidence Development Longitudinal Cohort Study</td>
<td>18,488</td>
<td>Dec 2018</td>
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<tr>
<td>NCT02008357a</td>
<td>Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study)</td>
<td>1150</td>
<td>Apr 2020</td>
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<tr>
<td>NCT02317250</td>
<td>Early and Long-Term Health Outcomes of Molecular Cerebral Imaging in Incipient Dementia (MCID) II</td>
<td>1500</td>
<td>Dec 2020</td>
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</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

References
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Beta-Amyloid Imaging with Positron Emission Tomography for Alzheimer Disease
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**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

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<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>78811</td>
<td>Positron emission tomography (PET) imaging; limited area (e.g., chest, head/neck)</td>
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<tr>
<td></td>
<td>78814</td>
<td>Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; limited area (e.g., chest, head/neck)</td>
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<td>HCPCS</td>
<td>A9586</td>
<td>Florbetapir F18, diagnostic, per study dose, up to 10 millicuries</td>
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<td></td>
<td>A9599</td>
<td>Radiopharmaceutical, diagnostic, for beta-amyloid positron emission tomography (PET) imaging, per study dose, not otherwise specified (<strong>Deleted code effective 1/1/2018</strong>)</td>
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<td>Q9982</td>
<td>Flutemetamol F18, diagnostic, per study dose, up to 5 millicuries</td>
</tr>
<tr>
<td></td>
<td>Q9983</td>
<td>Florbetaben F18, diagnostic, per study dose, up to 8.1 millicuries</td>
</tr>
</tbody>
</table>
6.01.55 Beta-Amyloid Imaging with Positron Emission Tomography for Alzheimer Disease

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<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td>ICD-10 Procedure</td>
<td>C030YZZ</td>
<td>Positron Emission Tomographic (PET) Imaging of Brain using Other Radionuclide</td>
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<td>ICD-10 Diagnosis</td>
<td>All Diagnoses</td>
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**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tr>
<td>09/27/2013</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/30/2015</td>
<td>Policy title change from Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer’s Disease Policy revision without position change</td>
<td>Medical Policy Committee</td>
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<td>01/01/2016</td>
<td>Coding update</td>
<td>Administrative Review</td>
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<td>07/01/2016</td>
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<tr>
<td>12/01/2016</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>11/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
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</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.