Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer Disease

Policy # 00381
Original Effective Date: 11/04/2013
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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers beta amyloid (Aβ) imaging with positron emission tomography (PET) to be investigational.*

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

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 Aβ 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, eg, 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 (eg, 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.

Positron emission tomography images biochemical and physiological functions by measuring concentrations of positron-emitting chemicals in the body region of interest. Radiopharmaceuticals used for
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Aβ 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 Aβ. However, due to their short half-life (20 minutes), $^{11}$C radiotracers are not convenient for commercialization. Several $^{18}$F Aβ radiotracers are currently in phase 2 and 3 clinical trials.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

In 2012, FDA approved flurbetapir F18 (Amyvid™; Avid Radiopharmaceuticals [a subsidiary of Eli Lilly], Philadelphia, PA)$^3$ as a radioactive agent for visualizing amyloid plaque in the brain. The FDA document prepared for the advisory committee meeting indicated that although flurbetapir 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.

In October 2013 and March 2014, FDA approved 2 other radioactive diagnostic imaging agents for detecting beta-amyloid plaque, flutemetamol F18 (Vizamyl™; GE Healthcare)$^3$ and flurbetaben F18 (Neuraceq™; Piramal Imaging, Matran, Switzerland)$^2$, 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 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.”
- Flurbetapir, flurbetaben, and flutemetamol are not intended for use in “predicting development of dementia or other neurological condition” or for “monitoring responses to therapies.”

Centers for Medicare and Medicaid Services (CMS)

In September 2013, the CMS issued a national coverage determination that provides limited coverage for the use of Aβ PET imaging in 2 scenarios: (1) clinically difficult differential diagnoses, such as AD versus 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. The CMS will cover 1 Aβ PET scan per patient in clinical studies that meet prespecified criteria.

**Rationale/Source**

This policy is updated annually with searches of the MEDLINE database. The most recent review covered the period through May 19, 2015. Studies of diagnostic tests can be divided into categories that are somewhat analogous to the phases designated in studies of pharmaceuticals (ie, phase 1 to phase 4). Different schemes have been proposed. In this Policy, we will use the following categorization: (1) phase 1...
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– technical performance; (2) phase 2 – diagnostic accuracy (sensitivity, specificity, positive and negative predictive value) in relevant populations of patients, such as those who have MCI or suspected AD; and (3) phase 3 – effect on patient outcomes, ie, demonstration that the diagnostic information can be used to improve patient outcomes.

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 (eg, conversion from MCI to probable AD) may be used as a surrogate end point to evaluate the diagnostic performance of Aβ imaging with PET.

Beta amyloid imaging may be particularly helpful for the future study of novel therapeutic agents that target amyloid plaques. However, current clinical purposes of testing for beta amyloid plaque density would be to improve diagnostic accuracy (eg, rule out AD) or predict conversion from MCI to AD. In general, evidence of a health benefit or clinical utility from testing requires demonstration that:

- Incremental improvements in diagnostic or prognostic accuracy over current practice occur, and
- Incremental improvements lead to improved health outcomes (eg, by informing clinical management decisions), and
- These outcomes may be obtained (ie, are generalizable) outside of the investigational setting.

A February 2013 Technology Evaluation Center (TEC) Assessment concluded that Aβ imaging with PET to evaluate suspected AD and other causes of cognitive decline does not meet the TEC criteria, based on a lack of direct evidence for clinical utility. The following is a summary of the main conclusions of the TEC Assessment:

“Studies have shown that florbetapir F18 PET results correlate with histopathologic findings at autopsy. This finding is important. Studies also have suggested that florbetapir F18 PET has some ability to differentiate between cognitively normal adults and patients with AD. However, the studies are limited by small sample sizes, differences in determining outcomes (eg, qualitative versus quantitative, unknown impact of training for physicians inexperienced with this modality), and the lack of evidence obtained from populations encountered in clinical practice. No information is available on the impact of this test on clinical outcomes, and few data are available on whether it can accurately identify patients with MCI who will develop AD.”

Technical Performance
Evidence on technical performance of this test should demonstrate that the test measures what it is intended to measure, ie, beta amyloid plaque. The best evidence on this would be direct comparison with a criterion standard test for measuring amyloid plaque, which is histopathologic examination of tissue. Other important measures of technical performance are the reliability of testing, including both test-retest reliability and interobserver reliability in reading test results.

Florbetapir
In August 2012, Clark et al published an extension of their pivotal study submitted to the FDA for the marketing application of florbetapir. This study reported on 59 participants with cognitive status ranging from normal to advanced dementia. Twelve participants had no cognitive impairment, 5 had MCI that did not meet the criteria for dementia, 29 had AD, and 13 had other forms of dementia. All patients had direct
measurement of amyloid burden by histopathologic examination, and images were interpreted by 3 readers using semiquantitative visual analysis on a scale of 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 Amyvid 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 below.

Data on technical performance of the test was included in a florbetapir pivotal study published in 2011. 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 passed away and were autopsied within 12 months of PET imaging; 29 were included in the primary efficacy analysis. This cohort comprised 9 patients (31%) 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 a non-AD dementia.

All patients had direct measurement of amyloid burden by histopathologic examination, and 52% met pathologic criteria for AD. A significant correlation of 0.78 was found between amyloid burden in the brain measured by Amyvid and the criterion standard of 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 specificity of 100% in this cohort, although it is noted that the young controls are outside of the intended use population.

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

Siderow 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 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 is limited by its small sample size and lack of histopathologic confirmation of probable dementia diagnoses.
Florbetaben
Information about a pivotal florbetaben study is provided in the prescribing information. Reliability and reproducibility of image interpretation was 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%). 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 ($\kappa=0.80$; 95% CI, 0.77 to 0.83) and for scans from 54 patients who underwent postmortem autopsy ($\kappa=0.75$; 95% CI, 0.67 to 0.83). Intrarreader reproducibility for 46 images ranged from 91% to 98% across the 5 readers.

In 2015, Sabri et al published an international, phase 3, histopathologic study of florbetaben-PET for detecting neuritic Aβ plaque (N=218). 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 threshold for sensitivity and specificity for detecting Aβ was determined by quantitative SUVR receiver operating characteristic (ROC) curve analysis. At the time of data analysis, 74 (36%) of 207 patients had died (57 with AD, 3 with Lewy body dementia, 6 with other dementias, 8 without dementia; mean age, 80 years). Mean time from PET scan to death was 329±272 days. 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 (sensitivity, 98% [95% CI, 94 to 100]; specificity: 89% [95% CI, 77 to 100]). Interrater agreement was high ($\kappa=0.90$ [95% CI, 0.81 to 0.98]). Using an optimized quantitative SUVR threshold, sensitivity was 89% (95% CI, 81 to 98) and specificity was 92% (95% CI, 82 to 100).

Flutemetamol
In 2015, Curtis et al published an international, phase 3, histopathologic, pivotal study of flutemetamol-PET for detecting neuritic Aβ plaque (N=203). 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 were included. PET images were read by 4 nuclear medicine physicians and 1 radiologist using a majority-read approach. Of 69 patients who died during the study (mean age, 81 years), 43 brains (63%) 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. Median sensitivity of flutemetamol-PET for Aβ was 88%, and median specificity was 88%. Interrater and intrarater agreement was high (Fleiss $\kappa=0.72$, Cohen $\kappa$ range, 0.60-1.00 across raters, respectively). The study is limited by the lack of MCI patients and use of majority rating for image interpretation.

$^{18}$F-Labeled Aβ Tracers
For all 3 Aβ radioactive tracers, FDA reported correlations between Aβ in PET scans and in histopathology specimens of 0.68 (95% CI, 0.43 to 0.82) to 0.76 (95% CI, 0.56 to 0.87) across brain regions.

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 varied from $\kappa$ 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>Table 1. Indirect Comparison of Beta-Amyloid PET Scan Reproducibility</th>
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<tbody>
<tr>
<td>Florbetapir</td>
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<tr>
<td>Mean (SD) test-retest variability of SUVR,$^a$ %</td>
</tr>
<tr>
<td>Interrater consistency of binary readings,$^b$$^\kappa$</td>
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</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.

Section Summary
Evidence on technical performance is mainly from pivotal studies. A strength of the florbetapir study was the comparison of imaging with the criterion standard of postmortem histopathology. Limitations included small sample sizes, a majority rating for assessing diagnostic accuracy, and having only 2 patients in the mildly impaired category, which is the population for whom the test is most likely to be used. Evidence from this study indicates that agreement between histopathology and beta amyloid testing by PET is good but not perfect. There is evidence for interobserver variability in reading the test; using a majority of 2/3 readers leads to a high agreement with histopathology. Studies of the technical performance of flutemetamol and florbetaben currently are unpublished. A summary review and prescribing information indicate that test-retest variability is low, and interrater reliability is sufficient.

Diagnostic Accuracy
The lack of a criterion standard for the diagnosis of AD that can be used in living patients is a barrier to high-quality research. The highest quality studies of diagnostic accuracy are those that use 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 in these studies is the patient population, which is not representative of the population for which the test is intended.

One of the studies that used this design was the 2011 pivotal study by Clark et al that reported on the diagnostic accuracy of florbetapir. 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. Sensitivity and specificity were calculated in comparison with the criterion standard of histopathology. In 46 participants with a scan-to-autopsy time of less than 12 months, sensitivity, specificity and accuracy were 96% (80-100), 100% (78-100), and 98% (87-100), respectively. For those with a scan-to-autopsy time of less than 2 years, sensitivity, specificity and accuracy were 92% (78-98), 100% (78-100), and 95% (85-99), respectively.

The pivotal study used a majority consensus of 3 independent reviewers as the final test reading; sensitivity and specificity were calculated in comparison with the criterion standard of histopathology. Of 15 patients who met pathologic criteria for AD, 14 had positive florbetapir scans (sensitivity, 93%). Of 14 patients who did not meet pathologic criteria for AD, all 14 had negative scans (specificity, 100%). Scans from all of the young patients (27 APOE4+ and 47 APOE–) were negative. Exploratory analysis indicated that in 3 patients (20%), clinical diagnosis did not match final autopsy diagnosis.
Another study that used autopsy as the criterion standard for diagnosis was the pivotal cohort study of flutemetamol. This study assessed diagnostic accuracy and reproducibility (both intra- and interreader) of flutemetamol PET imaging. In 68 patients 55 years of age or older who died within 13 months of imaging, clinical diagnoses were AD in 30 patients (44%), other cognitive disorders in 17 patients (25%), and no cognitive impairment in 21 patients (31%). Five readers blinded to clinical information interpreted PET images independently and in random order. Criterion standard was postmortem brain amyloid density; 43 (63%) were positive on histopathology review, and 25 (37%) were negative. Adequate sensitivity was defined as a lower bound of the 95% CI for sensitivity above 70% for at least 3 of the 5 readers. This criterion was met; median sensitivity was 88% (range, 81-93). Specificity, a secondary outcome, ranged from 44% to 92% with lower and upper 95% CI bounds ranging from 24% to 74% and 65% to 99%, respectively. Median specificity across the 5 readers was 88%. Interreader reproducibility met a prespecified minimum threshold of 0.6 for the lower 95% CI bound for the κ statistic; κ was 0.80 (95% CI, 0.79 to 0.86). Intrareader reproducibility on 29 duplicate images was high.

There was also 1 study using a pathologic criterion standard that evaluated the tracer florbetaben. This study evaluated 205 patients who had AD (69%), other non-AD dementia (15%), dementia with Lewy bodies (2%), or no clinical evidence of dementia (16%). Median patient age was 79 years (range, 48-98); 48% were female. Three trained readers, masked to clinical information, interpreted florbetaben-PET images, which were then compared with postmortem histopathology in patients who died during the study (n=82). In most patients (55%), PET images were obtained less than 1 year before death. At autopsy, 30 patients (37%) had 5 or fewer beta amyloid plaques by silver stain and were considered negative; 52 patients (63%) had more than 5 plaques and were considered positive. Median sensitivity across readers was 98% (range, 96-98), and median specificity was 80% (range, 77-83). In a subsequent study of images from the same 82 patients, 5 readers underwent electronic rather than in-person reader training. Median sensitivity across readers decreased to 96% (range, 90-100), and median sensitivity decreased to 77% (range, 47-80).

Other studies have used the clinical diagnosis of AD as the criterion standard, and therefore have been able to enroll patients similar to those seen in clinical care. 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. Quantitative SUVR thresholds were determined from the phase 3 trial previously described. Although there were significant differences in mean SUVRs across groups, there was considerable overlap in the range of values. The percentage of patients meeting threshold levels of amyloid with clinical AD, MCI, and cognitively healthy controls was 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 did not reach statistical significance.

In 2012, Camus et al reported on the diagnostic performance of florbetapir-PET in a clinical setting. Included were 13 patients with AD, 12 with MCI, and 21 older unimpaired controls. Positron emission tomography images were assessed visually by 2 readers who were blinded to clinical information and
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quantitatively by the SUVR of cortical regions compared with the cerebellum. Sensitivity and specificity were calculated based on clinical diagnosis as the comparison standard. Agreement in visual analysis between the 2 readers yielded a κ value of 0.71. Comparing visual assessment with initial clinical diagnosis, 11 of 13 AD patients (85%), 6 patients with MCI (50%), and 13 of 21 control patients (60%) had positive scans, resulting in a sensitivity of 84.6% and specificity of 38.1% for discriminating AD patients from controls. A quantitative assessment of the global cortex SUVR showed a sensitivity of 92.3% and specificity of 90.5% at a cutoff value of 1.12 (receiver operating characteristics area under the curve, 0.894). Although the study was limited by a small sample size and the use of clinical diagnosis as a reference standard, these results suggested a high number of false positives with visual assessment of the images. In addition, quantitative analysis was unable to differentiate patients with MCI from unimpaired controls.

In a follow-up to an earlier study, Doraiswamy et al (2014) compared cognitive decline in 47 patients with MCI who were beta amyloid-positive or beta amyloid-negative by flortbetapir-PET imaging. Over 36 months of follow-up, 6 (35%) of 17 beta amyloid-positive patients and 3 (10%) of 30 beta amyloid-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), a statistically nonsignificant difference (Fisher exact test, p=0.054). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for these outcomes combined were 67%, 71%, 35%, and 90%, respectively. This study is limited by its small sample size, use of a composite outcome, and lack of histopathologic confirmation of AD diagnoses.

In a study of 201 physicians who treated patients with probable AD (n=121) or healthy controls (n=80), Schipke et al (2012) reported sensitivity, specificity, PPV, and NPV of florbetaben-PET imaging of 82%, 83%, 47%, and 75%, respectively.

Ong et al (2014) compared florbetaben-PET SUVR (referenced to the cerebellar cortex) in 45 patients with MCI and a separate cohort of 15 patients with AD. Mean (SD) SUVR across 6 brain regions imaged was statistically higher in patients with AD compared with patients who had MCI (1.96 [0.27] vs 1.54 [0.27]; p<0.05). All patients with AD (100%) and 24 (53%) of 45 patients with MCI had high Aβ, defined by a cutoff value for mean SUVR of 1.45 or greater. Sensitivity, specificity, PPV, and NPV for discriminating AD from MCI were 100%, 47%, 38%, and 100%, respectively. This study was small, did not correct for multiple comparisons, and lacked histopathologic confirmation of AD diagnoses. In apparent 2- and 4-year follow-up 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 10% of 21 patients with baseline Aβ negative PET scans. PPV and NPV 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 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.

Section Summary
Evidence on the diagnostic performance of Aβ testing is limited, and available studies have methodologic issues, eg, small patient samples, that limit the validity of reported results. Some evidence suggests that there are a high number of false positive results in patients without AD. However, the pivotal study reported...
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high specificity, so the true rate of false positives is uncertain. Further high-quality studies using populations of patients that represent those presenting in clinical care are needed to better define the diagnostic performance of this test.

Effect on Patient Outcomes
No trials have been identified that reported health outcomes after beta amyloid PET imaging, thus there is no direct evidence for clinical utility.

Possible clinical uses of Aβ testing could include confirming the diagnosis of AD to begin medications at an earlier stage, or ruling out AD, which may lead to further diagnostic testing to determine the etiology of dementia and/or avoidance of anti-Alzheimer medications that would be unnecessary.

Since sensitivity and specificity of Aβ testing has not yet been established, it is not possible to determine an indirect chain of evidence that would indicate that health outcomes are improved. Because Aβ is present in elderly patients who do not have AD, it is unlikely that the test will have a high PPV, and, therefore it may have limited utility in confirming AD. It is possible that the NPV of testing may be high and that the test may be useful in ruling out AD. If this is true, it is uncertain how many patients would benefit from additional testing to determine etiology, or whether a substantial number of patients would avoid unnecessary medications that would otherwise be given.

Section Summary
Evidence on clinical utility, ie, that health outcomes are improved by testing, is lacking. There are no studies that report on clinical outcomes after testing. Diagnostic accuracy of testing is too uncertain to determine whether testing is likely to impact management and/or lead to improved outcomes.

Ongoing Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT02420756</td>
<td>Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study: A Coverage With Evidence Development Longitudinal Cohort Study</td>
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<td>Dec 2018</td>
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<td>NCT01518374a</td>
<td>Clinical Evaluation of Florbetapir F 18 (18F-AV-45)</td>
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<td>NCT02917250</td>
<td>Early and Long-Term Health Outcomes of Molecular Cerebral Imaging in Incipient Dementia (MCI-ID) II</td>
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<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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<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 2016</td>
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<td>NCT01703702a</td>
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Effectiveness of Florbetapir (18F) PET Imaging in Changing Patient Management and to Evaluate the Relationship Between Florbetapir (18F) PET Scan Status and Cognitive Decline

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

Summary

Literature on the use of Aβ PET imaging to aid in the diagnosis of patients with suspected AD is limited. A pivotal phase 3 trial, although to be commended for its use of the criterion standard of histopathology, had a number of limitations including small sample size, use of a majority rating of 3 physicians, and few patients in the mildly impaired category. This study reported a moderately high correlation of amyloid plaque with histopathologic examination. Sensitivity and specificity of this test have not yet been adequately determined in an appropriate population, including a larger number of patients with MCI.

Clinical utility of this technology is uncertain. The test is not likely to be useful for confirming AD in patients who present with cognitive impairment. It may have a role in ruling out AD, but this has yet to be established with certainty. Questions also remain about the use of this test outside of investigational settings, particularly regarding the accuracy of visual interpretation of images and how best to apply this test in routine clinical practice.

References

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14. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Beta Amyloid Imaging with Positron Emission Tomography (PET) for Evaluation of Suspected Alzheimer's Disease or Other Causes of Cognitive Decline. TEC Assessments Volume 27, Tab 5. PMID 21245183

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08/21/2013 Medical Policy Implementation Committee approval. New policy.
08/07/2014 Medical Policy Committee review

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08/20/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2015 Medical Policy Committee review
08/19/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2016 Coding update
08/04/2016 Medical Policy Committee review
08/17/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>78811, 78814</td>
</tr>
<tr>
<td>HCPCS</td>
<td>A9586, A9599, Q9982, Q9983</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>F02.80  G03.0  G03.1  G30.8  G30.9</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s); or

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer Disease

Policy #  00381
Original Effective Date:  11/04/2013
Current Effective Date:  10/22/2016

3. Reference to federal regulations.

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