6.01.55	Beta-Amyloid Imaging with Positron Emission Tomography for Alzheimer Disease		
Original Policy Date:	September 27, 2013	**Effective Date:**	November 1, 2020
Section:	6.0 Radiology	**Page:**	Page 1 of 20

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 mCi
- **Q9982**: Flutemetamol F18, diagnostic, per study dose, up to 5 mCi
- **Q9983**: Florbetaben F18, diagnostic, per study dose, up to 8.1 mCi

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 approved by the U.S. Food and Drug Administration. This technology is being evaluated to detect Aβ plaque density in adults with mild cognitive impairment (MCI) or dementia.

Related Policies

- Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease
- 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

Amyvid™, Vizamyl™, and Neuraceq™ (see Table 1) are approved by the U.S. Food and Drug Administration "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."[9,10,11]

Table 1. Agents Approved by the U.S. Food and Drug Administration

Agent	Trade Name	Manufacturer	NDA	Approved
florbetapir F18	Amyvid™	Avid Radiopharmaceuticals (subsidiary of Eli Lilly)	202008	2012
flutemetamol F18	Vizamyl™	GE Healthcare	203137	2013
florbetaben F18	Neuraceq™	Piramal Life Sciences	204677	2014

NDA: new drug application.

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 an atypical course or an etiologically mixed presentation (see Table 2).

Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. 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.[3] The range of beta-amyloid (Aβ) plaques and neurofibrillary tangles on histopathology may be described by the Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque density score, Thal stage, and Braak stage for neurofibrillary tangles. A histopathologic diagnosis must also take into account the age of the individual because neuritic plaques and tangles increase in cognitively normal elderly.

Table 2. Diagnosis of Alzheimer Disease

Diagnosis	Core Clinical Criteria[a]	Typical Course or Presentation[b]	Postmortem Confirmation[c]
Possible	Yes	No	NA
Probable	Yes	Yes	NA
Definite	Yes	May be typical or atypical	Yes

[a] Core clinical criteria: Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by

neuropsychological tests. The initial and most prominent cognitive deficits may be amnestic, which is the most common syndromic presentation of Alzheimer disease dementia, or alternatively language, visuospatial, or executive dysfunction. For nonamnestic presentations, deficits in other cognitive domains should be present.
[b] A typical clinical course is defined as an insidious onset, with the initial and most prominent cognitive deficits being either amnestic or nonamnestic (language, visuospatial, or executive dysfunction) and history of progressively worsening cognition over time.
[c] Presence of extracellular β-amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex.

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) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. The annual conversion rate of MCI to AD is between 5% and 10%.[5]

Assessment
Because clinical diagnosis can be difficult, particularly early in the course of the disease or with atypical dementia, 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). Aβ plaque is a requirement for the diagnosis of definite AD, but may also be 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.[6,7]

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.[8]

Literature Review
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Mild Cognitive Impairment
Clinical Context and Test Purpose
The purpose of beta-amyloid (Aβ) imaging with positron emission tomography (PET) in patients who have MCI is to determine the Aβ burden and determine the likelihood of developing Alzheimer disease (AD). There are currently no disease-modifying treatments for AD, and patients with MCI are typically not prescribed AD medications.

The question addressed in this evidence review is: Does Aβ PET imaging improve the net health outcome in patients with MCI?

The following PICO was used to select literature to inform this review.

Patients
The population of interest includes patients with MCI.

Interventions
The intervention of interest is Aβ imaging using a commercially available PET tracer (florbetapir F18, florbetaben F18, or flutemetamol F18).

The setting is a neurology or gerontology practice for patients undergoing evaluation for MCI.

Comparators
The criterion standard for the development of AD is postmortem neuropathologic examination. In the absence of comparisons with the criterion standard, a clinical follow-up to determine conversion to probable AD may be used as a surrogate endpoint to evaluate the diagnostic performance of Aβ imaging with PET.

Outcomes
Beneficial outcomes resulting from a true test result: The current clinical purpose of testing for Aβ plaque density would be to improve the prediction of conversion to AD. There are currently no disease-modifying treatments for AD.

Harmful outcomes resulting from a false test result: a false-positive test may result in failure to undergo additional testing for other causes of cognitive decline such as depression, obstructive sleep apnea, or drug-induced cognitive impairment; a false-negative test may lead to additional unnecessary tests (e.g., polysomnography) to evaluate these other potential causes of cognitive impairment.

Direct harms of the test: although generally well tolerated, there is a chance of adverse reactions to the radioligand.

Diagnostic accuracy can only be confirmed at autopsy or after several years of follow-up to monitor progression (or lack of progression) of disease. Conversion of MCI to AD has been shown to occur at a rate of 5% to 10% per year with conversion to any dementia at a rate of about 20% per year. Conversion of MCI to AD typically occurs in 2 to 3 years but may be as long as 8 years. Direct evidence of an improvement in health outcomes would be observed in years when a disease-modifying treatment has been developed.

Study Selection Criteria
For the evaluation of the clinical validity of the Aβ imaging, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard (conversion to probable AD)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Studies were excluded from the evaluation of the clinical validity of the Aβ test if they did not use the marketed version of the test, did not include information needed to calculate performance characteristics, did not use an appropriate reference standard or reference standard was unclear, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Multiple studies evaluating conversion from MCI to probable AD have been reported,[12.-19.] some of which are described in Tables 3 and 4. The largest prospective study was conducted by Wolk et al (2018), who reported that the hazard ratio for conversion to probable AD in patients with a baseline positive Aβ PET scan was 2.51 (p less than 0.001, see Table 4), increasing to 8.45 when low hippocampal volume and poorer cognitive status was added to the model.[16.]

In a retrospective cohort study of 250 patients with MCI, Jun et al (2019) reported progression to probable AD according to amyloid tertiles on PET scan conducted at baseline.[19.] Stages were defined as stage I, negative amyloid scan (global standardized uptake value ratio less than 1.11); stage II,1.11 to less than 1.30; stage III, 1.30 to less than 1.50; and stage IV, 1.50 or higher. The rates of progression to a diagnosis of dementia by 36 months (n=71 patients) were 2.2%, 15.5%, 32.9%, and 57.1% in stage I, II, III, and IV, respectively. In multivariate analysis, hazard ratios increased as the stage increased (stage II: 4.51; p = 0.015, stage III: 7.62; p = 0.001; stage IV: 9.42; p less than 0.001). The study authors concluded that large amyloid burden could be a predictor of fast cognitive decline in patients with MCI, but that more studies with longer follow-up times, more patients, and pathologic correlation are needed to define the role of amyloid PET imaging.

Table 3. Study Characteristics for Patients With Mild Cognitive Impairment

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Wolk et al (2018)[16.]	232 patients ≥55 y with MCI and no vascular, traumatic, or inflammatory causes	Prospective	Independent clinical adjudication committee	Visual rating as Aβ+ (n=98)	Every 6 mo for 3 y	Yes
Ong et al (2013, 2015)[14,15.]	45 patients with MCI	Prospective	Episodic memory Z score	SUVR ≥1.45 (n=24)	4 y	Yes (index); No (reference)
Doraiswamy et al (2014)[13.]	52 patients ≥50 y with recently diagnosed MCI	Longitudinal follow-up	4-point decline on the ADAS	Visual rating as Aβ+ (n=17) or Aβ- (n=30)	3 y	Yes

Aβ+: positive Aβ PET scan; Aβ-: negative Aβ PET scan: ADAS: Alzheimer Disease Assessment Scale; MCI: mild cognitive impairment; SUVR: standardized uptake value ratio.

Table 4. Clinical Validity for Patients With Mild Cognitive Impairment

Study	Initial N	Final N	Conversion of Aβ+ to pAD	Conversion of Aβ- to pAD	HR (95% CI) p	Clinical Validity, %			
						Sensitivity	Specificity	PPV	NPV
Wolk et al (2018[16.]	232	224	54% of 97	23% of 127	2.51(1.57 to 3.99) p less than 0.001	64	69	54	77
Ong et al (2013, 2015)[14,15.]	47	45	88% of 24	24% of 21		81	84	88	76

Study	Initial N	Final N	Conversion of Aβ+ to pAD	Conversion of Aβ- to pAD	HR (95% CI) p	Clinical Validity, %			
Doraiswamy et al (2014)[13]	52	47	35% of 17	10% of 30	p=0.054	67	71	35	90
Summary range			35%-88%	10%-24%	2.51	64-81	69-71	35-88	76-100

Aβ+: positive Aβ PET scan; Aβ- negative Aβ PET scan; CI: confidence interval; HR: hazard ratio;pAD: probable Alzheimer Disease; PPV: positive predictive value; NPV: negative predictive value.

Study limitations are summarized in Tables 5 and 6.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Wolk et al (2018)[16]		2. Used a majority rating of 5 readers instead of a single reviewer			
Ong et al (2013, 2015)[14,15]		2. Used SUVR or a majority rating of 5 readers	3. Used the episodic memory Z score rather than full clinical evaluation		
Doraiswamy et al (2014)[13]			3. Used a 4-point decline on ADAS rather than full clinical evaluation		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ADAS: Alzheimer Disease Assessment Scale; SUVR: standardized uptake value ratio.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 6. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Wolk et al (2018)[16]						1. CIs not reported
Ong et al (2013, 2015)[14,15]		1. Clinical evaluation at 4 y not blinded to PET scans				1. CIs not reported
Doraiswamy et al (2014)[13]						1. CIs not reported

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CI: confidence interval; PET: positron emission tomography.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective

publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Section Summary: Clinically Valid
One proposed use for Aβ imaging is to determine which patients with MCI have a likelihood of converting to AD. Studies have been conducted to evaluate the diagnostic accuracy of Aβ PET in patients with MCI, using conversion to probable AD as a reference standard. These studies have found that patients with a positive Aβ PET scan have a 2.5- to 7-fold increased risk of conversion to probable AD at 3 years. The clinical utility of this is uncertain. The negative predictive value of Aβ PET in these studies ranged from 77% to 95%.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

A multicenter RCT by Pontecorvo et al (2017) randomized 342 patients with MCI and 276 patients with AD and greater than 15% uncertainty in the diagnosis to immediate or delayed reporting of Aβ PET results to their physicians (see Table 7).[20] Changes in diagnosis and patient management are shown in Table 8. Health outcomes were evaluated at 1 year, but there were no statistical differences between groups for cognitive performance, function, or quality of life. However, due to the exploratory nature of the analysis and lack of power, it remains uncertain whether the changes in management affected health outcomes (see Tables 9 and 10). The progression of cognitive change did not differ between patients with MCI who had positive Aβ PET scan or a negative Aβ PET scan (p=0.568) over the year of the study.

Table 7. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	***Comparator***
Pontecorvo et al (2017)[20]	U.S., EU	60	2012-2015	618 patients 50-90 y with MCI (n=342) or dementia (n=276)	308 and physicians had immediate access to Aβ PET results	310 and physicians had delayed (12 mo) access to Aβ PET results

MCI: mild cognitive impairment; PET: positron emission tomography.

Table 8. Summary of Key Randomized Controlled Trial Results

Study	Change in Diagnosis	Change in Patient Management	Cognitive Performance	Function	Quality of Life
Pontecorvo et al (2017)[20]					
N	602	599	560	560	560
Immediate results, %	32.6	68	NR	NR	NR
Delayed results, %	6.4	55.5	NR	NR	NR
Diff/OR (95% CI)	Diff=26.2%	OR=1.70 (1.22 to 2.38)	NR	NR	NR
P	less than 0.001	less than 0.002	NR	NR	NR
NNT	3.8	8			

CI: confidence interval; Diff: difference; NNT: number needed to treat; NR: not reported; OR: odds ratio.

Notable limitations identified in each study are shown in Tables 9 and 10.

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Pontecorvo et al (2017)[20.]	1. Did not distinguish between patients with MCI or AD			1. Health outcomes were exploratory	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
AD: Alzheimer disease; MCI: mild cognitive impairment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Pontecorvo et al (2017)[20.]		1, 2. Not blinded to treatment or outcome assessment		6. Not intention-to-treat and number of unclear PET scans is not reported	3. Not powered for health outcomes	3. CIs and p values not reported for health outcomes

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CI: confidence interval; PET: positron emission tomography.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of Aβ PET has not been established, a chain of evidence supporting its clinical utility for this indication cannot be constructed.

Section Summary: Clinically Useful

Direct evidence on clinical utility is limited. One RCT reported on changes in diagnosis and management but did not find evidence that health outcomes (cognition, function, quality of

life) were improved by testing. A major limitation of this study is that the evaluation of health outcomes was exploratory and not sufficiently powered. No trials have been identified that reported whether changes in diagnosis are more accurate.

Dementia

Clinical Context and Test Purpose

The purpose of Aβ PET imaging is to determine the Aβ burden in patients who have dementia to aid a differential diagnosis between AD and non-AD causes of cognitive impairment and guide appropriate treatment. A negative Aβ PET scan could lead to further diagnostic testing to determine the etiology of dementia and/or avoidance of anti-Alzheimer medications that would be unnecessary.

There are currently no disease-modifying treatments for AD. For patients with mild-to-moderate dementia (Mini-Mental State Examination score of 10 to 26), a trial of acetylcholinesterase inhibitors (donepezil, rivastigmine or galantamine) may be given. Acetylcholinesterase inhibitors have a modest effect on cognitive performance, neuropsychiatric symptoms, and activities of daily living. Due to the difficulty in determining whether there has been a response to treatment, some providers recommend continuing treatment as long as the drugs are tolerable. Acetylcholinesterase inhibitors may also be prescribed for dementia with Lewy bodies but there is little support for the use of these drugs for other causes of dementia. The most common side effects are gastrointestinal (nausea, vomiting, diarrhea, anorexia, weight loss).

Memantine is an *N*-methyl-d-aspartate receptor antagonist and is thought to be neuroprotective. Memantine may be added to a cholinesterase inhibitor for moderate AD and has also been shown to have a modest benefit for cognition. Memantine may also be prescribed for vascular dementia. Memantine has fewer side effects than cholinesterase inhibitors but may increase agitation and delusional behaviors, particularly in patients with dementia with Lewy bodies.

The question addressed in this evidence review is: Does Aβ PET imaging improve the net health outcome in patients with dementia?

The following PICO was used to select literature to inform this review.

Patients

The population of interest includes patients with dementia.

Interventions

The intervention of interest is Aβ imaging using a commercially available PET tracer (florbetapir F18, florbetaben F18, or flutemetamol F18).

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

Comparators

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

Outcomes

Beneficial outcomes resulting from a true test result: improvement in cognition from acetylcholinesterase inhibitors or avoiding side effects from unnecessary treatment with acetylcholinesterase inhibitors; Identification and appropriate treatment of non-AD causes of dementia.

Harmful outcomes resulting from a false test result: side effects of incorrect or unnecessary treatment; not receiving correct treatment or failing to undergo additional testing such as formal neuropsychological testing and functional neuroimaging studies (e.g. single-photon emission computed tomography, perfusion magnetic resonance imaging, or fluorine 18 fluorodeoxy glucose PET) that evaluate areas of low metabolism or hypoperfusion and can help to distinguish AD from other causes of dementia.

Direct harms of the test: although generally well tolerated, there is a chance of adverse reactions to the radioligand.

Diagnostic accuracy can only be confirmed at autopsy or after a minimum of 3 years to monitor progression (or lack of progression) of disease. Direct evidence of an immediate effect of therapy is observable after 2 months of treatment with acetylcholinesterase inhibitors or memantine.

Study Selection Criteria
For the evaluation of the clinical validity of the Aβ imaging for suspected AD, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard (postmortem histopathologic confirmation or clinical follow-up)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Studies were excluded from the evaluation of the clinical validity of the test if they did not use the marketed version of the test, did not include information needed to calculate performance characteristics, did not use an appropriate reference standard or the reference standard was unclear, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist.

This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

A number of studies have demonstrated the reliability of florbetapir, florbetaben, and flutemetamol to detect Aβ in patients with an established diagnosis of AD compared with non-AD dementia or non-affected individuals.[21,-27,] In some studies, autopsy results were available to confirm the accuracy of the tracers to determine Aβ levels (see Table 11). These studies did not correlate Aβ PET scan results with a histopathologic diagnosis of AD. Further, these studies do not establish clinical validity in the intended use population, that is patients with suspected AD with an unclear or atypical presentation.

Table 11. Trial Results Using Aβ Plaque on Postmortem Histology as the Reference Standard

Study	n	Clinical Diagnosis	Interval From Imaging	Readers	Sensitivity (95% CI or Range), %	Specificity (95% CI or Range), %
Sabri et al (2015)[24] florbetaben	74	• AD • non-AD dementia • dementia with Lewy body • no evidence of dementia	11 mo[a]	3 readers	89 (81 to 98)	92 (82 to 100)
Curtis et al (2015)[25]; Salloway et al (2017)[26] flutemetamol	106	End-of-life cohort	7.5 mo[a]	Majority of 5 readers	86 to 92[b]	86 to 100[c]
Clark et al (2011, 2012)[21,22] florbetapir	59	End-of-life cohort	≤24 mo	Majority of 5 readers	92 (78-98)	100 (80-100)
Summary			7.5-24 mo	3-5 readers	86 to 93	86 to 100

Aβ:beta-amyloid; AD: Alzheimer disease; CI: confidence interval.
[a] Mean.
[b] Varied by criteria Aβ threshold.

An industry-funded multicenter study by Fleisher et al (2011) 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.[28] There were significant differences in mean standardized uptake value ratios across groups but 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. Among healthy controls, the percentage of patients with any florbetapir positivity on PET scan 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.

No studies on diagnostic accuracy were identified in the population of patients with suspected (possible) AD.

Section Summary: Clinically Valid
Aβ PET is proposed as a way to rule out AD in patients with an early or otherwise atypical presentation of dementia. Aβ plaque is only one of several markers of AD on histopathology but is necessary for a diagnosis of AD. A negative Aβ PET scan would, therefore, in theory, be associated with a lower likelihood of AD. Most studies evaluating the diagnostic accuracy of Aβ PET in patients with dementia have been conducted in patients at the end of life. Studies in patients with possible AD are needed

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

In the trial by Pontecorvo et al (2017; discussed above), 342 patients with MCI and 276 patients with dementia were randomized to immediate or delayed reporting of Aβ PET results to their physicians (see Table 7).[20] Changes in diagnosis and patient management are shown in Table 8. Prescription of acetylcholinesterase inhibitors decreased by 8%. The progression of cognitive

change did not differ between positive Aβ and negative Aβ patients with suspected AD (p=0.763) during the year of follow-up. Due to the lack of power, it remains uncertain whether the changes in management improved health outcomes (see Tables 9 and 10).

A number of multicenter studies have reported changes in diagnosis and patient management following Aβ PET imaging.[29,-34,] The largest prospective study to date is the Imaging Dementia—Evidence for Amyloid Scanning study, which assessed the association between Aβ PET imaging and subsequent changes in management among 11409 Medicare recipients.[34,] The primary endpoint was change in management between the pre- and post-PET visits, as assessed by a composite outcome that included Alzheimer disease drug therapy, other drug therapy, and counseling about safety and future planning. Changes between the pre-PET and post-PET composite management endpoint occurred in 60.2% (95%CI, 59.1%-61.4%) of patients with MCI and 63.5% (95%CI, 62.1%-64.9%) of patients with dementia. Physicians reported that PET results contributed substantially to the post-PET management plan in 85.2% of instances in which a change was made, and their diagnostic confidence in the uncertain range decreased from 72.4% to 16.2% at the post-PET-visit. One limitation of this study is that participants were mainly non-Hispanic whites, and thus were not reflective of the general population of Medicare beneficiaries or the US population.

In another recent study reported by Leuzy et al (2019), 207 patients with an initial diagnosis of MCI (63%) AD (20%), or subjective cognitive decline (2%) received Aβ PET imaging due to diagnostic uncertainty.[33,] Overall, Aβ PET led to a significant change in diagnosis (92 patients, 44%). The highest percentage change in diagnosis was observed in those with MCI (67 patients, 51%). The outcome of imaging led to more patients receiving treatment with cholinesterase inhibitors, from 34 patients prior to imaging to 109 after imaging. Of the 109 patients receiving cholinesterase inhibitor treatment, 93 (85%) were amyloid-positive. Treatment was discontinued following imaging in 1 amyloid-negative patient with MCI due to cholinergic side effects.

One potential use of Aβ PET imaging is to rule out AD, but studies have reported that the most common management change in response to an imaging result was to *increase* the use of medications to treat symptoms of Alzheimer disease. There were very few instances reported in which medication was discontinued or other interventions were avoided based on a negative PET result. Additionally, none of the studies evaluated whether changes in management improved patient health outcomes. It cannot be determined from these studies whether the revised diagnoses were correct, and without longer follow-up the effect of the management changes on health outcomes is uncertain.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of Aβ PET has not been established, a chain of evidence supporting its clinical utility for this indication cannot be constructed.

Section Summary: Clinically Useful
Direct evidence on clinical utility (i.e., improvement in net health outcomes resulting from testing) is lacking. Studies have reported a change in diagnosis and change in management but there is no evidence of an effect of Aβ PET on health outcomes. One potential use of Aβ PET imaging is to rule out AD, however, there were very few instances reported in which medication was discontinued or other interventions were avoided based on a negative PET result. The single RCT identified had insufficient power to determine the effect of Aβ imaging on health outcomes (i.e., quality of life, symptoms, function).

Summary of Evidence
For individuals who have MCI who receive Aβ imaging with PET, the evidence includes studies on diagnostic accuracy and a randomized controlled trial (RCT) that evaluated changes in

diagnosis and changes in management. Relevant outcomes are test performance measures, symptoms, and functional outcomes. Studies evaluating the diagnostic accuracy of Aβ PET in patients with MCI, using conversion to probable Alzheimer disease (AD) as a reference standard, report that patients with a positive Aβ PET scan at baseline have an increased risk of conversion to probable AD at 3 years. The negative predictive value of Aβ PET in these studies ranged from 77% to 95%. There are currently no disease-modifying drugs, and direct evidence of improved health outcomes with this technology is lacking. An RCT tested immediate vs delayed reporting of Aβ test results for patients with MCI and AD. No differences between the groups were found for health outcomes, although the study was not powered for these outcome measures. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have dementia who receive Aβ imaging with PET, the evidence includes studies on diagnostic accuracy and an RCT that evaluated changes in diagnosis and in management. Relevant outcomes are test performance measures, symptoms, and functional outcomes. One possible use of Aβ testing is as an adjunct to clinical diagnosis to rule out AD, which could lead to further diagnostic testing to determine the etiology of dementia and avoidance of unnecessary medications. The pivotal trials showed a sensitivity of 86% to 93% and a specificity of 86% to 100% compared with the criterion standard of Aβ plaque density on postmortem histology. However, the patients in these studies were at the end of life and not representative of the population of patients with suspected AD who present earlier in the course of the disease. Due to the lack of a criterion standard in living patients and limited follow-up, the sensitivity and specificity of Aβ PET in patients with suspected AD are unknown. Direct evidence of improved health outcomes with this technology is lacking. An RCT that tested immediate vs delayed reporting of Aβ test results for patients with MCI and AD found changes in diagnosis and management, but the effect of these changes on health outcomes such as quality of life, symptoms, and functional outcomes is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

Society of Nuclear Medicine and Molecular Imaging and Alzheimer's Association

The Appropriate Use Criteria (2013) for amyloid positron emission tomography were developed jointly by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association.[35,] They recommended that amyloid imaging as 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 apolipoprotein 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 of Neurological and Communicative Disorders & Stroke and Alzheimer Disease and Related Disorders Association

1984 Diagnostic Criteria

The National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association (1984) developed clinical criteria for the diagnosis of AD.[36] Although research to date continues to use the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association AD classification, in 2011, the National Institute on Aging and the Alzheimer's Association revised the diagnostic criteria for dementia due to AD.[1]

Table 12 summaries the 1984 guidelines as related to the diagnostic categories.

Table 12. The 1984 Diagnostic Categories for Alzheimer Disease

Diagnostic Categories for AD
Possible
Clinical diagnosis of possible AD: A. May be made on the basis of the dementia syndrome in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, the presentation, or the clinical course. B. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of dementia. C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.
Probable
Criteria for the clinical diagnosis of probable AD included: A. Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests; B. Deficits in 2 or more areas of cognition; C. Progressive worsening of memory and other cognitive functions; D. No disturbance of consciousness; E. Onset between ages 40 and 90 years, most often after the age of 65 years; and F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.
Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include: A. Plateaus in the course of progression of the illness; B. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sexual disorders, weight loss, and catastrophic verbal, emotional, or physical outbursts; C. Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder; and D. Seizures in advanced disease CT normal for age.
Features that make the diagnosis of probable AD uncertain or unlikely include: A. Sudden apoplectic onset; B. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and C. Seizures or gait disturbances at the onset or very early in the course of the illness.
Definite
Criteria for diagnosis of definite AD are: A. Clinical criteria for probable Alzheimer disease; AND B. Histopathologic evidence obtained from a biopsy or autopsy.

AD: Alzheimer Disease; CT: computed tomography.

National Institute on Aging and Alzheimer's Association
2011 Revised Diagnostic Criteria

In 2011, probable AD was defined by the National Institute on Aging and the Alzheimer's Association workgroup using the following diagnostic criteria[1]:

"Meets criteria for dementia … and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
B. Clear-cut history of worsening of cognition by report or observation; and
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
    a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
    b. Nonamnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem-solving. Deficits in other cognitive domains should be present.
D. The diagnosis of probable AD dementia should not be applied when there is evidence of:
    a. Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
    b. Core features of dementia with Lewy bodies other than dementia itself; or
    c. Prominent features of behavioral variant frontotemporal dementia; or
    d. Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or
    e. Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition."

All probable AD by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria are subsumed in the revised probable AD criteria. Revised criteria include a category of "Probable AD dementia with increased level of certainty" due to documented decline or having a causative AD genetic mutation. Additionally, a category "Probable AD dementia with evidence of the AD pathophysiological process" has been added. Evidence of the AD pathophysiologic process is supported by detection of low cerebrospinal fluid amyloid-β (Aβ) peptide 1-42, positive positron emission tomography amyloid imaging, or elevated cerebrospinal fluid tau, and decreased fluorine 18 fluorodeoxyglucose uptake on positron emission tomography in the temporoparietal cortex with accompanying atrophy by magnetic resonance imaging in relevant structures. Detection of the "pathophysiological process" is further divided by when in the disease natural history markers are expected to be detectable.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2013) 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 fronto-temporal 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 the Centers for Medicare & Medicaid Services-approved clinical trials of treatments or prevention strategies for AD. The Centers will cover one Aβ PET scan per patient in clinical studies that meet prespecified criteria.[37.]

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 13.

Table 13. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02008357[a]	Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study)	1150	Jul 2022
NCT02317250	Early and Long-Term Health Outcomes of Molecular Cerebral Imaging in Incipient Dementia (MCI-ID) II	1500	Dec 2022
NCT03444870[a]	Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of Gantenerumab in Patients With Early (Prodromal to Mild) Alzheimer's Disease	760	May 2023
NCT02781220	Implications for Management of PET Amyloid Classification Technology in the Imaging Dementia (IDEAS) Trial	69	Jul 2021
Unpublished			
NCT01886820[a]	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	290	Sep 2018 (Status unknown)

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

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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 codes does not constitute or imply member coverage or provider reimbursement.

Type	Code	Description
CPT®	78811	Positron emission tomography (PET) imaging; limited area (e.g., chest, head/neck)

Type	Code	Description
	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)
HCPCS	A9586	Florbetapir F18, diagnostic, per study dose, up to 10 mCi
	Q9982	Flutemetamol F18, diagnostic, per study dose, up to 5 mCi
	Q9983	Florbetaben F18, diagnostic, per study dose, up to 8.1 mCi

Policy History

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

Effective Date	Action
09/27/2013	BCBSA Medical Policy adoption
03/30/2015	Policy title change from Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer's Disease Policy revision without position change
01/01/2016	Coding update
07/01/2016	Coding update
11/01/2016	Policy title change from Beta Amyloid Imaging with Positron Emission Tomography for Alzheimer Disease
12/01/2016	Coding update
11/01/2017	Policy revision without position change
02/01/2018	Coding update
11/01/2018	Policy revision without position change
11/01/2019	Policy revision without position change
11/01/2020	Annual review. No change to policy statement. Policy guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 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.