6.01.55	Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease		
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Section:	6.0 Radiology	**Page:**	Page 1 of 34

Policy Statement

I. Amyloid beta imaging with positron emission tomography (PET) to predict conversion to Alzheimer disease is considered **investigational**.

II. Amyloid beta imaging with PET as an adjunct to clinical diagnosis in individuals with dementia is considered **investigational**.

III. Amyloid beta imaging with PET to select individuals with mild cognitive impairment or mild dementia due to Alzheimer disease for amyloid beta targeting plaque-therapy is considered **investigational**.

IV. Amyloid beta imaging with PET to evaluate individuals with mild cognitive impairment or mild dementia due to Alzheimer disease for continuation of amyloid beta plaque-targeting therapy is considered **investigational**.

V. PET Imaging with fluorine 18 fluorodeoxyglucose (FDG-PET) as an adjunct to clinical diagnosis in individuals with dementia is considered **investigational**.

VI. All other uses of amyloid beta imaging with PET are considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

This policy does not currently include tau PET imaging.

FDG-PET for individuals with suspected AD, previously included in Blue Shield of California Medical Policy: Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography, was added to this policy in October 2021.

Coding
See the Codes table for details.

Description

Alzheimer disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. 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 that can be imaged through positron emission tomography (PET).

Three radioactive tracers (florbetapir fluorine 18, florbetaben fluorine 18, flutemetamol fluorine 18) that bind to amyloid beta and can be detected in vivo with PET have been approved by the U.S. Food and Drug Administration (FDA) for amyloid beta imaging in patients who are being evaluated for cognitive decline.. Amyloid beta plaque PET imaging is proposed as an adjunct to the clinical

diagnosis of AD and as a component of identifying patients for amyloid beta plaque-targeting therapy.

Fluorine 18 fluorodeoxyglucose PET (FDG-PET) quantifies brain function by measuring glucose levels. FDG-PET is proposed as a method to distinguish AD from other dementias through identifying distinct regions of hypometabolism.

Related Policies

- Evaluation of Biomarkers for 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

Radiopharmaceuticals for PET Imaging
PET radiopharmaceuticals have been evaluated and approved as drugs by the FDA for use as diagnostic imaging agents. These radiopharmaceuticals are approved for specific conditions.

Amyvid™, Vizamyl™, and Neuraceq™ (Table 1) are approved by the FDA "for PET imaging of the brain to estimate amyloid beta neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline."[13,14,15,]

In 1994, the fludeoxyglucose (FDG) F18 radiotracer was originally approved by the FDA through the New Drug Application (NDA) process (NDA20306). The original indication was for "the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures." Added indications in 2000 were for "Assessment of glucose metabolism to assist in the evaluation of malignancy..." and "Assessment of patients with coronary artery disease and left ventricular dysfunction...." FDA approval of FDG does not include the evaluation of patients with cognitive decline. Multiple manufacturers have approved NDAs for FDG.

The prescribing information for all 3 agents used for amyloid beta imaging states:

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

Table 1. Radioactive Tracers Approved by the FDA for Amyloid Beta PET Imaging in Patents with Cognitive Impairment

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.

Rationale

Background

Alzheimer Disease

Alzheimer disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 12 million by 2050.[1]

The pathologic hallmarks of AD are extracellular deposits of amyloid beta, referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. There are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and how specifically they are pathophysiologically associated with AD is not well understood. Generally referred to as "amyloid hypothesis", it is believed that aggregation of amyloid beta oligomers in the brain leads to amyloid plaques and is thought to be the primary driver of the disease process. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.[2,3]

Role of Positron Emission Tomography

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 that can be imaged through positron emission tomography (PET). These biomarkers include amyloid beta plaque and glucose metabolism in the brain. PET images biochemical and physiologic functions by measuring concentrations of radioactive chemicals that have been partially metabolized in a particular region of the body. Radiopharmaceuticals used for PET imaging may be generated in a cyclotron or nuclear generator and introduced into the body by intravenous injection.

Demonstration of amyloid beta 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.[4,5,6] 18-F FDG PET quantifies brain function by measuring glucose levels. Through identifying distinct regions of hypometabolism, FDG-PET is proposed as a method to distinguish AD from other dementias, especially in patients with atypical presentations (e.g., younger age).[7]

PET imaging in patients with mild cognitive impairment (MCI) or dementia is intended to provide a more accurate diagnosis earlier in the disease course than clinical diagnosis alone, resulting in earlier, appropriately targeted treatment and other management approaches.

Treatment Options

Current treatment goals for patients with AD are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Treatment remains largely supportive, including creation and implementation of individualized dementia care plans, caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (e.g., adult day care, caregiver training, etc).[8,] Non-pharmacologic treatments include physical activity,[9,10,] as well as behavioral strategies to ameliorate neuropsychiatric symptoms (e.g., agitation, delusions, disinhibition), and problem behaviors (e.g., resistance to care, hoarding, obsessive-compulsive behaviors).[11,]

FDA-approved drugs for AD symptoms include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine and the N-methyl-D-aspartate antagonist, memantine. These drugs, either alone or in combination, focus on managing cognitive and functional symptoms of the disease and have not been shown to alter disease trajectory. The evidence for efficacy is limited and these agents are associated with significant side effects.[11,12,]

In June 2021, aducanumab (Aduhelm; Biogen) was approved by the FDA for treatment of AD. This indication was approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with aducanumab. Continued approval for this indication is contingent upon verification of clinical benefit in confirmatory trial(s).The FDA, under the accelerated approval regulations (21 CFR 601.41), requires that Biogen conduct a randomized, controlled trial to evaluate the efficacy of aducanumab compared to an appropriate control for the treatment of AD. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The expected date of trial completion is August 2029 and final report submission to the FDA by February 2030.

In July 2021, FDA amended the approved label to emphasize the disease stages studied in the clinical trials. The amended label states, "Treatment with aducanumab should be initiated in patients with MCI or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied."

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.

Amyloid Beta Imaging With Positron Emission Tomography to Predict Conversion to Alzheimer Disease in Patients with Mild Cognitive Impairment

Clinical Context and Test Purpose

The purpose of amyloid beta imaging with positron emission tomography (PET) in patients who have mild cognitive impairment (MCI) is to determine the amyloid beta burden and the likelihood of developing Alzheimer disease (AD).

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

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

Populations
The relevant population of interest is individuals with MCI.

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

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 to evaluate the diagnostic performance of amyloid beta imaging with PET.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, functional outcomes, health status measures, and quality of life.

Beneficial outcomes resulting from a true test result: The current clinical purpose of testing for amyloid beta plaque density would be to improve the prediction of conversion to 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 (eg, 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.

Study Selection Criteria
For the evaluation of the clinical validity of amyloid beta 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 amyloid beta 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.

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).

Review of Evidence

Systematic Reviews

Martinez et al conducted 3 Cochrane systematic reviews of the diagnostic accuracy of PET scan using florbetapir, florbetaben, and flutemetamol to detect people with MCI who will clinically progress to AD or other forms of dementia at follow-up (Table 2). The reviews included 1 study of florbetaben,[18,] 2 studies of flutemetamol ,[19,20,] and 3 studies of florbetapir.[21,22,23,]

Study characteristics, results, and methodological limitations are summarized in Table 2. The reviewers concluded that due to limited data available, varying sensitivity and specificity, and risk of bias limiting confidence in the conclusions, routine use of the technology could not be recommended.

Table 2. Systematic Reviews of the Diagnostic Accuracy of PET Imaging to Predict Progression to AD

Study	Literature Search Dates	Populations	Interventions	Studies Included (N)	Study Designs Included	Reference Standard	Follow-up Duration	Results-Progression from MCI to AD		Methodological Limitations of Included Studies
								By Visual Assessment	By SUVR > 1.45	
Martinez et al (2017a)][24,]	1946 to May 2017	Participants recruited and clinically classified as having MCI at time of performing the test. Diagnosis of MCI established using the Petersen criteria or revised Petersen criteria.	18F PET with florbetaben	1 (N=45)	Longitudinal studies with prospectively defined cohorts with any accepted definition of MCI at time of performing the scan and a reference standard	Progression to the target conditions evaluated by a physician with expertise in the dementia field	2 to 4 years	Sensitivity 100% (95% CI, 84% to 100%) Specificity 83% (95% CI, 63% to 95%)	Sensitivity 100% (95% CI, 84% to 100%) Specificity 88% (95% CI, 68% to 97%)	High risk of bias: Lack of information about participant selection; reference standard was made with knowledge of the medical studies and medical records; conflicts of interest
Martinez et al (2017b) [25,]	Same as above	Same as above	18F PET with flutemetamol	2 (N=243)	Same as above	Same as above	3 years	Sensitivity 64% (95% CI, 53 to 75) Specificity 69% (95% CI, 60 to 76)	Sensitivity 89% (95% CI, 52% to 100%) Specificity 80% (95% CI, 44% to 97%)	Uncertainty about the clinical diagnosis of AD; not a clear definition of a positive index test in one study; the reference standard in one study was not explicitly described; potential conflict of interest with the company that produced the

Study	Literature Search Dates	Populations	Interventions	Studies Included (N)	Study Designs Included	Reference Standard	Follow-up Duration	Results-Progression from MCI to AD	Methodological Limitations of Included Studies
									tracer in both studies
Martinez et al (2017c)[26,]	Same as above	Same as above	18F PET with florbetapir	2 (N=448)	Same as above	Same as above	1. *Follow-up from 2 to < 4 years:* Sensitivity 67% (95% CI, 30% to 93%) Specificity 71% (95% CI, 54% to 85%) *Follow-up from 1 to < 2 years:* Sensitivity 89% (95% CI, 78% to 95%) Specificity 58% (95% CI, 53% to 64%)	*Follow-up from 1 to < 2 years (n=401, 1 study):* Sensitivity 87% (95% CI, 76% to 94%) Specificity of 51% (95% CI, 45% to 56%)	Uncertainty about the clinical diagnosis of AD; lack of information regarding the selection of participants; not clear if the reference standard interpretation was made without knowledge of the PET scan results in 2 studies; potential conflict of interest with the company that produced the tracer

AD: Alzheimer disease; CI: confidence interval; MCI: mild cognitive impairment; PET: positron emission tomography; SUVR: standardized uptake value ratio.

Nonrandomized Studies

Additional studies evaluating conversion from MCI to probable AD have been published following the Cochrane systematic reviews.[27,28,29,30,] The largest prospective study was reported by Wolk et al (2018) (Tables 3 and 4).[31,] The hazard ratio for conversion to probable AD at 3 years in patients with a baseline positive amyloid beta PET scan was 2.51 (95% confidence interval [CI], 1.57 to 3.99; p <.001), increasing to 8.45 when low hippocampal volume and poorer cognitive status was added to the model.

Table 3. Study Characteristics for Patients With MCI

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Wolk et al (2018)[31,]	232 patients ≥ 55 years of age with MCI and no vascular, traumatic, or inflammatory causes	Prospective	Independent clinical adjudication committee	Visual rating as amyloid beta+ (n=98)	Every 6 months for 3 years	Yes

amyloid beta+: positive amyloid beta PET scan; MCI: mild cognitive impairment.

Table 4. Clinical Validity for Patients With MCI

Study	Initial N	Final N	Conversion of amyloid	Conversion of amyloid	HR (95% CI); p	Clinical Validity, %

			beta+ to probable AD	beta- to probable AD					
						Sensitivity	Specificity	PPV	NPV
Wolk et al (2018)[31,]	232	224	54% of 97	23% of 127	2.51 (1.57 to 3.99); p <.001	64	69	54	77

AD: Alzheimer disease; amyloid beta+: positive amyloid beta PET scan; amyloid beta-: negative amyloid beta PET scan; CI: confidence interval; HR: hazard ratio; NPV: negative predictive value; PPV: positive 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)[31,]		2. Used a majority rating of 5 readers instead of a single reviewer			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[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)[31,]						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.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, 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.

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.

Review of Evidence

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 randomized controlled trials (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 amyloid beta PET results to their physicians (Table 7).[32,] 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 (Tables 9 and 10). The progression of cognitive change did not differ between patients with MCI who had a positive amyloid beta PET scan or a negative amyloid beta PET scan (p=.568) over the year of the study.

Table 7. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Pontecorvo et al (2017)[32,]	U.S., EU	60	2012-2015	618 patients 50-90 years of age with MCI (n=342) or dementia (n=276)	Physicians had immediate access to amyloid beta PET results (n=308)	Physicians had delayed (12 months) access to amyloid beta PET results (n=310)

EU: European Union; MCI: mild cognitive impairment; PET: positron emission tomography; RCT: randomized controlled trial.

Table 8. Summary of Key RCT Results

Study	Change in Diagnosis	Change in Patient Management	Cognitive Performance	Function	Quality of Life
Pontecorvo et al (2017)[32,]					
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 value	<.001	<.002	NR	NR	NR
NNT	3.8	8			

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

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)[32,]	1. Results 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)[32],		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 amyloid beta PET has not been established, a chain of evidence supporting its clinical utility for this indication cannot be constructed.

Section Summary: Amyloid Beta Imaging With Positron Emission Tomography to Predict Conversion to Alzheimer Disease in Patients with Mild Cognitive Impairment

One proposed use for amyloid beta 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 amyloid beta PET in patients with MCI, using conversion to probable AD as a reference standard. Systematic reviews of these studies have concluded that limited data, varying sensitivity and specificity, and risk of bias limited confidence in conclusions. In a more recent prospective study of 224 individuals with MCI, the hazard ratio for conversion to probable AD at 3 years in patients with a baseline positive amyloid beta PET scan was 2.51 (95% CI, 1.57 to 3.99; p <.001), with a negative predictive value of 77%. The clinical utility of this is uncertain. 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.

Amyloid Beta Imaging With Positron Emission Tomography as an Adjunct to Clinical Assessment to Diagnose Alzheimer Disease in Patients with Dementia

Clinical Context and Test Purpose

One proposed use of amyloid beta PET imaging in patients with dementia is to determine the amyloid beta burden to aid a differential diagnosis between AD and non-AD causes of cognitive impairment and guide appropriate treatment and/or further testing. Amyloid PET may be positive in cognitively normal subjects who do not develop AD and in patients with other forms of non-AD dementia; therefore, the value of beta PET imaging would be to rule out a diagnosis of AD in patients with dementia. A negative amyloid beta 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. U.S. Food and Drug Administration (FDA)-approved drugs for AD symptoms include cholinesterase inhibitors donepezil, rivastigmine, and galantamine, the N-methyl-D-aspartate antagonist, memantine, and the amyloid beta targeting therapy, aducanumab. Cholinesterase inhibitors are indicated in mild, moderate, and severe AD, while memantine is approved for moderate-to-severe AD. These drugs, either alone or in combination, focus on managing cognitive and functional symptoms of the disease and have not been shown to alter disease trajectory. The evidence for efficacy is limited and these agents are associated with significant side effects.
The question addressed in this evidence review is: Does amyloid beta PET imaging improve the net health outcome in patients with dementia being assessed for AD?

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

Populations
The population of interest is patients with dementia.

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

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 to evaluate the diagnostic performance of amyloid beta PET imaging.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, functional outcomes, health status measures, and quality of life.

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 (eg, single-photon emission computed tomography [SPECT], perfusion magnetic resonance imaging, or fluorine 18 fluorodeoxyglucose [FDG] 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 amyloid beta 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.

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).

Review of Evidence

Nonrandomized Trials

A number of studies have demonstrated the reliability of florbetapir, florbetaben, and flutemetamol to detect amyloid beta in patients with an established diagnosis of AD compared with non-AD dementia or non-affected individuals.[33,34,35,36,37,38,39,] In some studies, autopsy results were available to confirm the accuracy of the tracers to determine amyloid beta levels (Table 11). These studies did not correlate amyloid beta 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 Amyloid Beta 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)[36,] florbetaben	74	• AD • non-AD dementia • dementia with Lewy body • no evidence of dementia	11 months[a]	3 readers	89 (81 to 98)	92 (82 to 100)
Curtis et al (2015)[37,]; Salloway et al (2017)[38,] flutemetamol	106	End-of-life cohort	7.5 months[a]	Majority of 5 readers	86 to 92[b]	86 to 100[b]
Clark et al (2011, 2012)[33,34,] florbetapir	59	End-of-life cohort	≤24 months	Majority of 5 readers	92 (78 to 98)	100 (80 to 100)
Summary			7.5 to 24 months	3 to 5 readers	86 to 93	86 to 100

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

Bao et al (2021) reported on a study of PET amyloid imaging in 109 consecutive patients referred to a memory clinic in Hong Kong.[40,] Subjects underwent clinical assessment and the local version of the Montreal Cognitive Assessment. The mean (standard deviation [SD]) composite standardized uptake

value ratio (SUVR) values for patients with a diagnosis of subjective cognitive decline, MCI, AD, and non-AD dementia were 0.50 (0.80), 0.53 (0.16), 0.76 (0.10), and 0.56 (0.16), respectively. With adjustment for age and sex, AD had significantly higher global amyloid beta retention than subjective cognitive decline (p <.0001), MCI (p <.0001), and other dementias (p <.001), while the remaining 3 groups showed no significant difference. Based on the established threshold (SUVR of 0.62) used for differentiating positive and negative scans in global binding, approximately 28% of MCI subjects had a positive global amyloid beta burden, while 91% of AD and 31% of other dementia subjects had a positive PET scan. The authors concluded that quantitative global and regional amyloid beta binding by 18F-flutemetamol PET could be used to discriminate between AD and MCI with 100% sensitivity, 69% specificity, and 79% accuracy.

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.

Review of Evidence

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 amyloid beta PET results to their physicians (Table 7).[32,] 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 amyloid beta and negative amyloid beta patients with suspected AD (p=.763) during the year of follow-up. Due to the lack of power, it remains uncertain whether the changes in management improved health outcomes (Tables 9 and 10).

A number of multicenter studies have reported changes in diagnosis and patient management following amyloid beta PET imaging.[41,42,43,44,45,46,] The largest prospective study to date is the Imaging Dementia—Evidence for Amyloid Scanning study, which assessed the association between amyloid beta PET imaging and subsequent changes in management among 11,409 Medicare recipients.[46,] The primary endpoint was change in management between the pre- and post-PET visits, as assessed by a composite outcome that included AD 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% to 61.4%) of patients with MCI and 63.5% (95% CI, 62.1% to 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 White patients, 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 amyloid beta PET imaging due to diagnostic uncertainty.[45,] Overall, amyloid beta 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 amyloid beta 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 AD. 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.

Section Summary: Amyloid Beta Imaging With Positron Emission Tomography as an Adjunct to Clinical Assessment to Diagnose Alzheimer Disease in Patients with Dementia

Amyloid beta PET is proposed as a way to rule out AD in patients with an early or otherwise atypical presentation of dementia. Amyloid beta plaque is only one of several markers of AD on histopathology but is necessary for a diagnosis of AD. A negative amyloid beta PET scan would, therefore, in theory, be associated with a lower likelihood of AD. Most studies evaluating the diagnostic accuracy of amyloid beta PET in patients with dementia have been conducted in patients at the end of life. Additional, well-designed studies in patients with possible AD are needed. Direct evidence on clinical utility (ie, 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 amyloid beta PET on health outcomes. One potential use of amyloid beta 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 amyloid beta imaging on health outcomes (ie, quality of life, symptoms, function).

Amyloid Beta Imaging With Positron Emission Tomography to Select Patients for Targeting Therapy

Clinical Context and Test Purpose

The purpose of amyloid beta imaging with PET in individuals with a clinical diagnosis of MCI or mild dementia due to AD is to guide a decision about initiation of amyloid beta plaque-targeting therapy. The test is intended to exclude patients with clinically diagnosed MCI/AD that are not amyloid positive, and to select for treatment those amyloid positive subjects that are potentially able to benefit from treatment.

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

Populations

The relevant population of interest is individuals with a clinical diagnosis of MCI or mild dementia who are being considered for an FDA-approved amyloid beta plaque-targeting therapy.
The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before symptoms arise.[47,]The National Institute on Aging and the Alzheimer's Association have created a "numeric clinical staging scheme" (Table 12) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia. This numeric cognitive staging scheme is not designed to be used in a clinical setting but to be used for interventional trials such as those of aducanumab. The phase 3 RCTs for aducanumab were stratified to include 80% of stage 3 patients and 20% of stage 4 patients. This numeric staging scheme is very similar to the categorical system for staging AD outlined in the FDA guidance for industry pertaining to developing drugs for treatment of early AD.[48,]

Table 12. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum[a]

Stage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Severity	Pre-clinical	Pre-clinical	MCI due to Alzheimer disease	Mild Dementia	Moderate Dementia	Severe Dementia

Stage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Clinical Features	• Performance within expected range on objective cognitive tests. • No evidence of recent cognitive decline or new neurobehavioral symptoms.	• Normal performance within expected range on objective cognitive tests. • Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months). • Mild neurobehavioral changes may coexist or may be the primary complaint rather than cognitive. • No functional impact on daily life activities.	• Performance in the impaired/abnormal range on objective cognitive tests. • Evidence of decline from baseline. • Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life.	• Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. • Clearly evident functional impact on daily life, affecting mainly instrumental activities. • No longer fully independent/requires occasional assistance with daily life activities.	• Progressive cognitive impairment or neurobehavioral changes. • Extensive functional impact on daily life with impairment in basic activities. • No longer independent and requires frequent assistance with daily life activities.	• Progressive cognitive impairment or neurobehavioral changes. • Clinical interview may not be possible. • Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

Adapted from Table 6, Jack et al (2018)[49,]
[a]Applicable only to individuals in the Alzheimer continuum that fall into 1 of the 4 biomarker groups: 1) A+T+N+ 2) A+T-N- 3) A+T+N- 4) A+T-N+ where A: Aggregated amyloid beta or associated pathologic state (CSF amyloid $beta_{42}$, or amyloid $beta_{42}$/amyloid $beta_{40}$ ratio or Amyloid PET), T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau or Tau PET) and N: Neurodegeneration or neuronal injury (anatomic MRI, FDG PET or CSF total tau)
For stages 1 to 6: Cognitive test performance may be compared to normative data of the investigators choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.
For stages 2 to 6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.
For stages 3 to 6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.
AD: Alzheimer disease; CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

Interventions

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

Comparators

The comparator of interest is standard clinical management without amyloid beta imaging. A definitive diagnosis of AD requires histopathologic examination of brain tissue obtained by biopsy or autopsy. In practice, clinical criteria based on clinical examination, neurologic and neuropsychological examinations, and interviews with informants (eg, family members or caregivers) are used to diagnose AD by excluding other diseases that can cause similar symptoms and distinguish AD from other forms of dementia.

Outcomes

The general outcomes of interest are disease-specific survival, overall survival, test validity, symptoms, change in disease status, functional outcomes, health status measures, and quality of life. Follow-up at 2 to 5 years is of interest to monitor outcomes.

Amyloid beta PET is intended to identify patients with the required plaques that are targeted by the therapy. Therefore, response to therapy is the outcome of interest. Important outcomes to measure response include cognitive, functional, and quality of life outcomes.

As per the FDA 2018 draft guidance for developing drugs for treatment of early AD, treatment for mild to moderate AD dementia (corresponding to stages 4 and 5) would be considered substantially effective if there is improvement on a core symptom (eg, a measure of cognition) and a global clinical measure (eg, a clinician's judgement of change) or a functional measure (eg, activities of daily living).[48,] For studies including prodromal patients with MCI (corresponding to Stage 3 in the FDA 2018 draft guidance), the FDA requires only a statistically significant change on a prespecified composite measure that includes cognition and daily function combined, as a demonstration of substantial effectiveness. In the 2013 draft guidance, the agency specifically recommended the Clinical Dementia Rating Sum of Boxes (CDR-SB) as a composite measure that had shown validity and reliability for this purpose. No quantified minimum differences were specified but the rationale was that such a composite measure serves as an indicator of change in both the core or cognitive outcome.[50,] Meeting minimal clinically important difference (MCID) thresholds, however, are not requisites for the FDA to conclude a trial shows substantial effectiveness or to authorize marketing approval.[51,]

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Clinical Validity

The clinical validity of amyloid beta PET in patients with suspected AD is addressed above in this review. Most studies evaluating the diagnostic accuracy of amyloid beta PET in patients with dementia have been conducted in patients at the end of life. Studies in patients with possible AD are needed.

Clinical Utility

Evidence about the clinical utility of amyloid beta PET imaging to select patients for treatment with amyloid beta targeting-therapy is available from 4 studies conducted as part of the clinical development program for aducanumab (Table 13). PRIME was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging, staggered study conducted in the United States with the primary objectives of safety and tolerability. The phase 3 studies were multicenter, global, randomized, double-blind, placebo-controlled studies of identical design with the primary objective of efficacy and safety. In all 3 studies, the diagnosis of AD was confirmed by presence of amyloid pathology measured by 18-florbetapir PET imaging. The pivotal trials ensured enrollment of patients at an earlier stage of their disease (MCI due to AD or mild AD dementia based on an entry criteria).[52,] This section briefly summarizes these studies. For a more detailed discussion of the evidence see Policy 5.01.38 - Aducanumab for Alzheimer Disease.

Table 13. Summary of the Clinical Development Program for Aducanumab

Trial	NCT	Phase	Description	N	Design	Status
PRIME (Study 3)	NCT01677572	1	Evaluate safety and tolerability of multiple doses of aducanumab in prodromal or mild AD	196	DB RCT	Completed and published

Trial	NCT	Phase	Description	N	Design	Status
ENGAGE (Study 301)	NCT02477800	3	Evaluate safety and tolerability of aducanumab in early AD	1647	DB RCT	Completed and unpublished
EMERGE (Study 302)	NCT02484547	3	Evaluate safety and tolerability of aducanumab in early AD	1638	DB RCT	Completed and unpublished
EMBARK	NCT04241068	3	Evaluate long-term safety and tolerability of aducanumab in participants enrolled in previous trials of aducanumab (EMERGE, ENGAGE, the LTE of the PRIME study, and EVOLVE)	2400	Open-label	Ongoing

AD: Alzheimer disease; DB: double-blind; LTE: long-term extension; RCT: randomized controlled trial.
The phase 3 studies randomized patients to aducanumab low dose (3 or 6 mg/kg for *ApoE ε4* carriers and noncarriers, respectively), aducanumab high dose (10 mg/kg), or placebo every 4 weeks for 18 months, followed by an optional, dose-blind, long-term extension period. Due to early termination and consequent administrative censoring, data were missing for up to 45% of patients randomized in the 2 trials. Approximately, 60% of patients had the opportunity to complete week 78 of the trial before the trials were terminated for futility.[52,]

Study 302 (N=1638 randomized patients) met the primary endpoint in patients treated with high-dose aducanumab (10 mg/kg) with an absolute difference of -0.39 in favor of aducanumab on the 18-point CDR-SB scale (a relative 22% less decline in high dose aducanumab group compared to placebo, p=.0120). The reported MCID is generally considered to be 1 to 2 points on a scale from 0 to 18.[53,] Results of a responder analysis describing the proportion of individuals who achieved a predefined level of improvement were not reported. Results in the low-dose aducanumab (3 or 6 mg/kg for *ApoE ε4* carriers and noncarriers, respectively) group were not statistically significant compared with placebo (absolute difference, -0.26 ; relative difference, -15% ; p=.0901) and therefore no statistically valid conclusions can be made for any of the secondary endpoints for either treatment arm.

Study 301 (N=1647 randomized patients) did not meet its primary end point of a reduction relative to placebo in the CDR-SB score. For the high-dose arm, an absolute difference of 0.03 and a relative difference of 2% favored placebo (p=.8330). For the low-dose arm, an absolute difference of -0.18 and a relative difference of 12% favored aducanumab (p=.8330). Because of the pre-specified plans to control for type I error for multiple comparisons, no statistically valid conclusions can therefore be made for any of the secondary endpoints.[52,]

Change in brain amyloid signal was measured by florbetapir fluorine 18 PET and quantified by a composite SUVR in a subset of sites and patients (n=488) at week 78. In study 302, adjusted mean change from baseline to week 78 relative to placebo showed a dose-dependent reduction in amyloid beta by -0.179 and -0.278 in the low- and high-dose arms, respectively. In study 301, adjusted mean change from baseline to week 78 relative to placebo showed a dose-dependent reduction in amyloid beta by -0.167 and -0.232 in the low- and high-dose arms, respectively. While aducanumab showed statistically significant dose dependent changes from baseline in amyloid beta plaques, there are no satisfactory data clearly establishing that individual changes in amyloid correlate with or predict long term cognitive and functional changes as measured by CDR-SB. The FDA statistical review[54,] reported no correlation in study 302 between reduction in amyloid plaque and long term clinical change among the high-dose cohort or full 10 mg/kg dosed subgroup. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that observed reduction in amyloid will translate into a clinical benefit to patients.

Data with limited follow-up are available to analyze safety because the phase 3 trials were stopped prematurely due to futility. Pooled safety data from the 2 phase 3 clinical trials showed that about 35% (compared to 3% in the placebo arm) of patients on aducanumab experienced amyloid-related

imaging abnormalities (ARIA), whose clinical effects can range from asymptomatic to severe. Although the majority of patients were asymptomatic or had symptoms such as headache, confusion, or dizziness that resolved with temporary stoppage of the drug, 6.2% of participants receiving the high dose of aducanumab discontinued the drug due to ARIA.[55,]

An increase in falling adverse events was observed in the high-dose group as compared to placebo across the 2 phase 3 studies (15% vs. 12%, respectively). FDA statistical review[54,] reported a hazard ratio of 1.33 (p=.016) suggesting a 33% relative increase in hazard of falling for 10 mg/kg compared to placebo.

Section Summary: Amyloid Beta Imaging With Positron Emission Tomography to Select Patients for Targeting Therapy

For individuals with a clinical diagnosis of MCI or mild dementia due to AD who are being considered for an FDA-approved amyloid beta plaque-targeting therapy, the evidence includes 2 RCTs and 1 dose-finding and proof of concept phase I trial. ENGAGE (study 301) and EMERGE (study 302) were identical randomized, double-blind, placebo-controlled studies that enrolled patients with early AD. Both trials were terminated early following a prespecified interim analysis for futility. In study 301, there was no treatment benefit observed in either the high- or low-dose arms at week 78. In study 302, a statistically significant difference in change from baseline in CDR-SB was observed in the high-dose arm (difference vs. placebo, -0.39 [95% CI, -0.69 to -0.09]) but not the low-dose arm at week 78. The observed change of 0.39 was well below the range of 1 to 2 points reported as the MCID in published literature. Approval by the FDA was based on the reduction in amyloid plaques, which was observed in both trials and at all doses. However, there are no satisfactory data clearly establishing that individual changes in amyloid correlate with or predict long term cognitive and functional changes. In the absence of clinical data convincingly demonstrating cognitive and functional effects, it cannot be concluded that the observed reduction in amyloid will translate into a clinical benefit to patients. Pooled safety data showed that about 35% of patients on aducanumab experienced ARIA; the risk of falling was also increased with aducanumab. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health benefit of aducanumab in patients with early AD.

Amyloid Beta Imaging With Positron Emission Tomography to Evaluate Patients Receiving Targeting Therapy for Continuation of Treatment

Clinical Context and Test Purpose

The purpose of amyloid beta imaging with PET is to guide decisions about continuation or discontinuation of amyloid beta plaque-targeting therapy.

The question addressed in this evidence review is: Does amyloid beta imaging with PET improve the net health outcome in patients who are receiving disease targeting therapy for AD?
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with MCI or early AD who are being treated with amyloid beta plaque-targeting therapy.

Interventions

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

Comparators

The comparator of interest is standard clinical management without amyloid beta imaging. The decision to continue or discontinue treatment would be based on clinical factors.

Outcomes
The general outcomes of interest are disease-specific survival, overall survival, test validity, symptoms, change in disease status, functional outcomes, health status measures, and quality of life. Follow-up at 2 to 5 years is of interest to monitor outcomes.

Amyloid beta PET is intended to identify patients with the required plaques that are targeted by the therapy. Therefore, response to therapy is the outcome of interest. Important outcomes to measure response include cognitive, functional, and quality of life outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
No studies addressing the use of amyloid beta PET imaging to monitor response to amyloid beta targeting-therapy were identified. The aducanumab product label recommends monitoring for ARIAs using magnetic resonance imaging (MRI), but does not address monitoring amyloid beta using PET.

Section Summary: Amyloid Beta Imaging With Positron Emission Tomography to Evaluate Patients Receiving Targeting Therapy for Continuation of Treatment
No evidence was identified.

Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography to Confirm a Diagnosis of Alzheimer Disease
Clinical Context and Test Purpose
The purpose of fluorine 18 fluorodeoxyglucose PET (FDG-PET) in patients with suspected AD is to confirm a diagnosis of AD.

The question addressed in this evidence review is: Does the use of FDG-PET improve the net health outcome in individuals with suspected AD?

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

Populations
The population of interest is patients with suspected AD.
A definitive diagnosis of AD requires histopathologic examination of brain tissue obtained by biopsy or autopsy. In practice, clinical criteria based on clinical examination, neurologic and neuro-psychological examinations, and interviews with informants (eg, family members or caregivers) are used to diagnose AD by excluding other diseases that can cause similar symptoms and distinguish AD from other forms of dementia.

Interventions
The intervention of interest is FDG-PET. FDG-PET quantifies brain function by measuring glucose levels. Through identifying distinct regions of hypometabolism, FDG-PET is proposed as a method to distinguish AD from other dementias, especially in patients with atypical presentations such as younger age.

For patients with suspected AD, FDG-PET would be performed following inconclusive clinical examinations and standard radiographs.

Comparators
Clinical diagnosis without FDG-PET is currently being used for suspected AD.

Outcomes
For patients with suspected AD, the main outcomes of interest are test validity, symptoms, change in disease status, functional outcomes, health status measures, and quality of life.

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

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.
- Included a validation cohort separate from development cohort.

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).

Review of Evidence
Systematic Reviews
Summaries of the characteristics and results of several meta-analyses of the early diagnosis of AD in people with cognitive impairment or for differentiating between potential causes of dementia are shown in Tables 14 and 15, and are briefly described below.

Table 14. Characteristics of Systematic Reviews on FDG-PET for Diagnosing AD and Dementia

Study	Dates	Studies	N (Range)	Design	Outcomes
Zhu et al (2022)[56,]	Up to 2020	16	NR	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Smailagic et al (2015)[57,]	1999-2013	16	697 (19-94)	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Davison et al (2014)[58,]	Up to 2013	9	NR	OBS	Diagnostic accuracy for diagnosis of AD, differential diagnosis in dementia, predicting conversion from MCI to AD
Bloudek et al (2011)[59,]	1990-2010	119	NR	OBS	Diagnostic accuracy for diagnosis of AD, differential diagnosis in dementia
Yuan et al (2009)[60,]	2001-2005	6	280 (17-128)	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Matchar et al (2001)[61,]	1995-2001	18	1018 (10-138)	OBS	Diagnostic accuracy for distinguishing AD from healthy controls and for differential diagnosis in dementia

AD: Alzheimer disease; FDG-PET: fluorine 18 fluorodeoxyglucose positron emission tomography; MCI: mild cognitive impairment; NR: not reported; OBS: observational.

Zhu et al (2022) conducted a meta-analysis of cerebral perfusion imaging methods (FDG-PET, SPECT, and MRI) in the assessment of MCI conversion to AD. A total of 16 studies were included (5 with FDG-PET).[56,] The authors found significantly higher sensitivity, specificity, and positive likelihood

ratio with FDG-PET than SPECT or MRI. The studies for FDG-PET were determined to have low risk of bias.

Smailagic et al (2015) conducted a Cochrane review to assess the diagnostic accuracy of FDG-PET for detecting people who clinically convert to AD or other forms of dementia at follow-up.[57,] Included studies evaluated the diagnostic accuracy of FDG-PET to determine the conversion from MCI to AD or to other forms of dementia. Sixteen studies (N=697 participants) were included in the qualitative review and 14 studies (n=421 participants) were included in the analysis. Because there are no accepted thresholds to define positive findings based on PET scans and studies used mixed thresholds for diagnosis, reviewers used a hierarchical summary receiver operating characteristic curve to derive pooled estimates of performance characteristics at fixed values. Results are shown in Table 15. Five studies evaluated the accuracy of FDG-PET for all types of dementia. The sensitivities ranged between 46% and 95% while the specificities ranged between 29% and 100%; however, a meta-analysis could not be conducted because of the small study sample sizes. Reviewers indicated that most studies were poorly reported and had an unclear risk of bias, mainly for the reference standard and participant selection domains.

In a systematic review (quality assessment of included studies was not reported), Davison et al (2014) reported on studies on the diagnostic performance of FDG-PET and SPECT identified through PubMed.[58,] Three studies (197 patients) used histopathology as the reference standard. In patients with or without a clinical diagnosis of AD, sensitivity was 84% and specificity was 74%. In patients with memory loss or dementia, sensitivity was 94% and specificity was approximately 70%. In patients undergoing evaluation for dementia, sensitivity was 94% and specificity was 73%. Precision estimates were not given. In 3 different studies (271 participants), the sensitivities and specificities of FDG-PET for distinguishing AD from Lewy body dementia ranged from 83% to 99% and from 71% to 93%, respectively. In 2 studies (183 participants), for predicting conversion from MCI to AD, sensitivity and specificity of PET ranged from 57% to 82% and from 67% to 78%, respectively.

Bloudek et al (2011) assessed diagnostic strategies for AD in a meta-analysis.[59,] Reviewers included 119 studies of diagnostic performance characteristics published from 1990 to 2010. Studies were identified through a search of PubMed and included imaging, biomarkers, and clinical diagnostic strategies. Twenty studies included performance characteristics of FDG-PET for diagnosing AD compared with normal, nondemented controls. Thirteen studies described characteristics of FDG-PET for diagnosing AD compared with demented controls. FDG-PET demonstrated the highest area under the receiver operating characteristic curve, sensitivity, and specificity among all of the diagnostic methods for distinguishing AD from normal controls, but one of the lowest receiver operating characteristic curves comparing AD with non-AD demented controls (excluding MCI), due primarily to the low specificity in this group. Results are shown in Table 15.

In a meta-analysis, Yuan et al (2009) compared the prognostic capacity of FDG-PET, SPECT, and structural MRI to predict patients' conversion from MCI to AD.[60,] Using 24 articles (N=1112 patients) published between 1990 to 2008 (6 studies with 280 patients on FDG-PET, published between 2001-2005), reviewers found no statistically significant difference among the 3 modalities in pooled sensitivity, pooled specificity, or negative likelihood ratio. Results are shown in Table 15. There was strong evidence of between-study heterogeneity and marked asymmetry in the funnel plot (with studies missing from the bottom left quadrant), indicating possible publication bias of studies with null results. Efforts to identify sources of heterogeneity (eg, publication year, age, male-female ratio, follow-up interval, years of education, mean Mini-Mental State Examination score at baseline) yielded no significant results.

Using decision-analysis modeling, Matchar et al (2001) performed a technology assessment for the Agency for Healthcare Research and Quality to examine whether the use of FDG-PET would improve health outcomes for diagnosis of AD in 3 clinical populations: patients with dementia, patients with MCI, and subjects with no symptoms, but with a first-degree relative with AD.[61,] For the review, a

search was performed using PubMed, CINAHL, and the HealthSTAR databases. Eighteen articles (N=1018 participants) were included. The reference standard used in the studies was either histopathology or clinical diagnosis. Studies reported on various cutoffs for PET positivity, and, therefore, an unweighted summary receiver operating characteristic method was used to calculate the pooled area under the curve. Results are summarized in Table 15. Reviewers concluded that outcomes for all 3 groups were better if all patients were treated with agents such as cholinesterase inhibitors rather than limiting treatment to patients based on FDG-PET results. The rationale was that the complications of treatment were relatively mild, and that treatment was considered to have some degree of efficacy in delaying the progression of AD.

Table 15. Results of Systematic Review on Use Assessing FDG-PET for AD and Dementia

Study	Studies	N	Outcomes	Estimate (95% CI)
Zhu et al (2022)[56,]	5[a]	NR	Diagnostic accuracy	• Sensitivity: 87.2% (81.3% to 92.1%) • Specificity: 89.35% (77.6% to 91.8%) • PLR: 5.973 (3.15 to 6.72) • NLR: 0.132 (0.05 to 0.49)
Smailagic et al (2015)[57,]	14	421	Diagnostic accuracy	• Sensitivity range: 25% to 100% • Specificity range: 15% to 100% • PLR: 4.03 (2.97 to 5.47) • NLR: 0.34 (0.15 to 0.75)
Davison et al (2014)[58,]	3	197	Diagnostic accuracy	• Sensitivity: 84% • Specificity: 74%
•	2	183	Diagnostic accuracy, predicting conversion from MCI to AD	• Sensitivity range: 57% to 82% • Specificity range: 67% to 78%
•	5	292	Diagnostic accuracy, differentiating AD and LBD	• Sensitivity range: 83% to 92% • Specificity range: 67% to 93%
Bloudek et al (2011)[59,]	20	NR	Diagnostic accuracy	• Sensitivity: 90% (84% to 94%) • Specificity: 89% (81% to 94%)
•	13	NR	Diagnostic accuracy, AD vs. other dementia	• Sensitivity: 92% (84% to 96%) • Specificity: 78% (69% to 85%)
Yuan et al (2009)[60,]	6	280	Diagnostic accuracy	• Sensitivity: 89% (92% to 94%) • Specificity: 85% (78% to 90%) • PLR: 4.6 (3.2 to 6.7) • NLR: 0.15 (0.05 to 0.48)
Matchar et al (2001)[61,]	15	729	Diagnostic accuracy	• Sensitivity: 88% (79% to 94%) • Specificity: 87% (77% to 93%)
•	3	289	Diagnostic accuracy, distinguishing AD from non-AD dementia	• Sensitivity range: 86% to 95% • Specificity range: 61% to 74%

AD: Alzheimer disease; CI: confidence interval; FDG-PET: fluorine 18 fluorodeoxyglucose positron emission tomography; LBD: Lewy body dementia; MCI: mild cognitive impairment; NLR: negative likelihood ratio; NR; not reported; PLR: positive likelihood ratio.
[a] Includes only the 5 studies with FDG-PET.

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.

Review of Evidence

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.

Motara et al (2017) assessed the accuracy of dual-trained radiologists and nuclear medicine physicians to diagnose the type of cognitive impairment based on FDG-PET/computed tomography (CT) images. Records of patients who had undergone FDG-PET/CT because of cognitive impairment (AD, frontotemporal dementia, mixed dementia, and dementia with Lewy bodies) following a negative CT or MRI scans were reviewed (N=136).[62,] Questionnaires were sent to the referring physicians to gather information on the final clinical diagnosis, usefulness of the PET/CT report, and whether the report impacted clinical management. The response rate was 72% (98/136) and mean patient follow-up was 471 days. For the diagnosis of AD, using the final clinical diagnosis as the reference standard, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 87%, 97%, 93%, and 91%, respectively. Questionnaires received from the 98 physicians indicated that PET/CT: was useful (78%); had an impact on clinical management (81%); added confidence to the pretest clinical diagnosis (43%); reduced the need for further investigations (42%); changed the pretest clinical diagnosis (35%); and led to a change in therapy (32%).

Section Summary: Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography to Confirm a Diagnosis of Alzheimer Disease

Several systematic reviews offer evidence on FDG-PET for diagnosing AD in people with cognitive impairment and for differentiating between AD and other dementias. Studies included in these reviews were generally poor quality. There is no standard cutoff for positive amyloid findings on PET scanning for diagnosing AD, and many studies did not include postmortem confirmation of AD as the reference standard. These limitations lead to uncertainty about estimates of performance characteristics. Although it appears that FDG-PET has high sensitivity and specificity, the evidence does not compare the performance characteristics of clinical diagnosis with PET to clinical diagnosis without PET, so the incremental value of adding PET to the standard clinical diagnosis is unclear. No studies reported on clinical outcomes of patients diagnosed with versus without FDG-PET. A single study was identified that surveyed physicians on the clinical utility of FDG-PET/CT in managing patients with cognitive impairment. In general, the physicians found the FDG-PET/CT helpful but no clinical outcomes of patients were reported.

Summary of Evidence

For individuals who have MCI who receive amyloid beta imaging with PET to predict conversion to AD, the evidence includes studies on diagnostic accuracy and a RCT that evaluated changes in diagnosis and management. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, and quality of life. Studies have been conducted to evaluate the diagnostic accuracy of amyloid beta PET in patients with MCI, using conversion to probable AD as a reference standard. Systematic reviews of these studies have concluded that limited data, varying sensitivity and specificity, and risk of bias limited confidence in conclusions. In a more recent prospective study of 224 individuals with MCI, the hazard ratio for conversion to probable AD at 3 years in patients with a baseline positive amyloid beta PET scan was 2.51 (95% CI, 1.57 to 3.99; p <.001), with a NPV of 77%. Direct evidence of improved health outcomes with this technology is lacking. A RCT tested immediate versus delayed reporting of amyloid beta test results for patients with MCI and AD. No differences between the groups were found for health outcomes, although the study was not powered for these outcome measures. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have dementia who receive amyloid beta imaging with PET as an adjunct to clinical diagnosis, the evidence includes studies on diagnostic accuracy and a RCT that evaluated

changes in diagnosis and management. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, and quality of life. One possible use of amyloid beta testing is as an adjunct to clinical diagnosis to rule out AD ; this could lead to further diagnostic testing to determine the etiology of dementia, and potentially facilitate avoidance of inappropriate presumptive medication use and/or appropriate use of medications for other types of dementia. The pivotal trials showed a sensitivity of 86% to 93% and a specificity of 86% to 100% compared with the criterion standard of amyloid beta plaque density on postmortem histology. However, the patients in these studies were at the end of life and not representative of the population of patients with suspected AD who present earlier in the course of the disease. Due to the lack of a criterion standard in living patients and limited follow-up, the sensitivity and specificity of amyloid beta PET in patients with suspected AD are unknown. Direct evidence of improved health outcomes with this technology is lacking. A RCT that tested immediate versus delayed reporting of amyloid beta test results for patients with MCI and AD found changes in diagnosis and management, but the effect of these changes on health outcomes such as quality of life, cognitive and behavioral symptoms, and functional outcomes is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a clinical diagnosis of MCI or mild dementia due to AD who are being considered for an FDA-approved amyloid beta plaque-targeting therapy, the evidence includes 2 RCTs and 1 dose-finding and proof of concept phase I trial of aducanumab. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, quality of life, disease-specific survival, and overall survival. ENGAGE (study 301) and EMERGE (study 302) were identical randomized, double-blind, placebo-controlled studies that enrolled patients with early AD. Both trials were terminated early following a prespecified interim analysis for futility. In study 301, there was no treatment benefit observed in either the high- or low-dose arms at week 78. In study 302, a statistically significant difference in change from baseline in CDR-SB was observed in the high-dose arm (difference vs. placebo, -0.39 [95% CI, -0.69 to -0.09]) but not the low-dose arm at week 78. The observed change of 0.39 was well below the range of 1 to 2 points considered the MCID. Approval by the FDA was based on reduction in amyloid plaques, which was observed in both trials and at all doses. However, there are no satisfactory data clearly establishing that individual changes in amyloid beta plaque correlate with or predict long-term cognitive and functional changes. In the absence of clinical data demonstrating cognitive and functional effects, it cannot be concluded that the observed reduction in amyloid will translate into a clinical benefit to patients. Pooled safety data showed that about 35% of patients on aducanumab experienced ARIA; an increased risk of falling was also observed. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health benefit of aducanumab in patients with early AD. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with early AD (MCI or mild dementia due to AD) who are being treated with amyloid beta plaque-targeting therapy and are being evaluated for continuation of therapy, no evidence was identified on the role of subsequent or repeat amyloid beta PET imaging or its correlation with clinical assessment of disease status. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, quality of life, disease-specific survival, and overall survival. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected AD who receive FDG-PET to diagnose AD, the evidence includes systematic reviews of nonrandomized studies. Relevant outcomes are test validity, symptoms (cognitive and/or behavioral), change in disease status, functional outcomes, health status measures, and quality of life. The studies included in the reviews were generally of poor quality. There is no standard cutoff for FDG-PET positivity for diagnosing AD, and many studies have not included postmortem confirmation of AD as the reference standard, leading to uncertainty about estimates of performance characteristics. FDG-PET may have high sensitivity and specificity for diagnosing AD,

but there is little evidence comparing the performance characteristics of clinical diagnosis using FDG-PET with the clinical diagnosis not using FDG-PET. Therefore, the incremental value of adding FDG-PET to the standard clinical diagnosis is unclear. No studies have reported on clinical outcomes of patients diagnosed with and without FDG-PET. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology

The American College of Radiology appropriateness criteria for dementia, revised in 2019, state that amyloid positron emission tomography (PET) and fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) may be appropriate for initial imaging of patients with cognitive decline and suspected Alzheimer disease (AD).[63,]

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

The Appropriate Use Criteria (2013) for amyloid PET were developed jointly by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association.[64,] They recommended that amyloid imaging is appropriate for individuals with all of the following characteristics:
"(i) a cognitive complaint with objectively confirmed impairment; (ii) AD [Alzheimer disease] as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert; and (iii) when knowledge of the presence or absence of AD pathology is expected to increase diagnostic certainty and alter management."
Appropriate candidates include:

1. Patients with unexplained persistent or progressive MCI [mild cognitive impairment]
2. Patients satisfying core clinical criteria for possible AD, but are unusual in the clinical presentation
3. Patients with progressive dementia and atypically early age of onset (eg, 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) $\varepsilon 4$
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 (eg, legal, insurance coverage, or employment screening)."

U.S. Preventive Services Task Force Recommendations

In 2020, the USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for cognitive impairment in older adults (I statement).[65,]

Medicare National Coverage

Amyloid Beta Positron Emission Tomography Imaging

The Centers for Medicare & Medicaid Services (CMS; 2013) issued a national coverage determination, through coverage with evidence development, that provides limited coverage for the use of amyloid beta PET imaging in 2 scenarios: (1) clinically difficult differential diagnoses, such as AD versus frontotemporal dementia, when the use of amyloid beta 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 1 amyloid beta PET scan per patient in clinical studies that meet prespecified criteria.[66,]

Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography

CMS (2004) released a national coverage decision for a subset of patients "with a recent diagnosis of dementia and documented cognitive decline of at least 6 months, who meet diagnostic criteria for both [Alzheimer disease] and frontotemporal dementia, who have been evaluated for specific alternative neurodegenerative diseases or causative factors, and for whom the cause of the clinical symptoms remains uncertain." [67,]

The National Coverage Determination for FDG-PET for dementia and neurodegenerative diseases (220.6.13) states that:

"Medicare covers FDG Positron Emission Tomography (PET) scans for either the differential diagnosis of frontotemporal dementia (FTD) and Alzheimer's disease (AD) under specific requirements; OR, its use in a Centers for Medicare & Medicaid Services (CMS)-approved practical clinical trial focused on the utility of FDG PET in the diagnosis or treatment of dementing neurodegenerative diseases." [68,] Specific requirements for each indication are clarified in the document.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 16.

Table 16. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05108922[a]	A Phase 3, Open-Label, Parallel-Group, 2-Arm Study to Investigate Amyloid Plaque Clearance With Donanemab Compared With Aducanumab-avwa in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 4)	200	Jul 2024
NCT05457998	BioFINDER-Brown: Examination of Alzheimer's Disease Biomarkers	200	Sept 2027
NCT05508789[a]	Global Study to Investigate Safety and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 5)	800	Jul 2025
NCT02008357[a]	Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study)	1150	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	1016	Oct 2026
NCT04437511[a]	Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 2)	1800	Aug 2025
NCT04468659[a]	AHEAD 3-45 Study: A Placebo-Controlled, Double-Blind, Parallel-Treatment Arm, 216 Week Study to Evaluate Efficacy and Safety of Treatment With BAN2401 in Subjects With Preclinical Alzheimer's Disease and Elevated Amyloid (A45 Trial) and in Subjects With Early Preclinical Alzheimer's Disease and Intermediate Amyloid (A3 Trial)	1400	Oct 2027
NCT03860857	MRI and PET Biomarkers for Cognitive Decline in Older Adults	200	Dec 2024
NCT04669028[a]	A Phase 3, Double Blind, Randomized, Placebo Controlled, Parallel Group, Multicenter Study of NE3107 in Subjects Who Have Mild to Moderate Alzheimer's Disease	316	Jan 2023

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03887455[a]	A Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study With an Open-Label Extension Phase to Confirm Safety and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease	1906	Sept 2025
NCT04241068[a]	A Study to Evaluate Safety and Tolerability of Aducanumab in Participants With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205	1696	Feb 2025
NCT04426539	New IDEAS: Imaging Dementia-Evidence for Amyloid Scanning Study - A Study to Improve Precision in Amyloid PET Coverage and Patient Care	7000	Dec 2024
Unpublished			
NCT02781220	Implications for Management of PET Amyloid Classification Technology in the Imaging Dementia (IDEAS) Trial	69	Jul 2021 (last update Jan 2020)

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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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)
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.
12/01/2021	Annual review. Policy statement and guidelines updated. Policy title changed from Beta-Amyloid Imaging with Positron Emission Tomography for Alzheimer Disease to current one.
12/01/2022	Annual review. Policy statement and Literature review updated.
12/01/2023	Annual review. No change to policy statement.
09/01/2024	Annual review. No change to policy statement. Policy guidelines 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 and Feedback (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.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease 6.01.55 **Policy Statement:** I. Amyloid beta imaging with positron emission tomography (PET) to predict conversion to Alzheimer disease is considered **investigational**. II. Amyloid beta imaging with PET as an adjunct to clinical diagnosis in individuals with dementia is considered **investigational**. III. Amyloid beta imaging with PET to select individuals with mild cognitive impairment or mild dementia due to Alzheimer disease for amyloid beta targeting plaque-therapy is considered **investigational**. IV. Amyloid beta imaging with PET to evaluate individuals with mild cognitive impairment or mild dementia due to Alzheimer disease for continuation of amyloid beta plaque-targeting therapy is considered **investigational**. V. PET Imaging with fluorine 18 fluorodeoxyglucose (FDG-PET) as an adjunct to clinical diagnosis in individuals with dementia is considered **investigational**. VI. All other uses of amyloid beta imaging with PET are considered **investigational**.	**Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease 6.01.55** **Policy Statement:** I. Amyloid beta imaging with positron emission tomography (PET) to predict conversion to Alzheimer disease is considered **investigational**. II. Amyloid beta imaging with PET as an adjunct to clinical diagnosis in individuals with dementia is considered **investigational**. III. Amyloid beta imaging with PET to select individuals with mild cognitive impairment or mild dementia due to Alzheimer disease for amyloid beta targeting plaque-therapy is considered **investigational**. IV. Amyloid beta imaging with PET to evaluate individuals with mild cognitive impairment or mild dementia due to Alzheimer disease for continuation of amyloid beta plaque-targeting therapy is considered **investigational**. V. PET Imaging with fluorine 18 fluorodeoxyglucose (FDG-PET) as an adjunct to clinical diagnosis in individuals with dementia is considered **investigational**. VI. All other uses of amyloid beta imaging with PET are considered **investigational**.