Medical Policy

BlueCross BlueShield Kansas
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Title: Positron Emission Tomography (PET) Selected: Technologies for Evaluation of Alzheimer Disease

Related Policies:	▪ *Monoclonal Antibodies for Treatment of Alzheimer Disease*

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Populations	Interventions	Comparators	Outcomes
Individuals: • With mild cognitive impairment to aid in prognosis	Interventions of interest are: • Amyloid beta imaging with positron emission tomography to predict conversion to Alzheimer disease	Comparators of interest are: • Clinical diagnosis alone • Postmortem histopathology	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life
Individuals:	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include:

Populations	Interventions	Comparators	Outcomes
• With dementia to aid in diagnosis	• Amyloid beta imaging with positron emission tomography as an adjunct to clinical diagnosis	• Clinical diagnosis alone • Postmortem histopathology	• Test validity • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life
Individuals: • With mild cognitive impairment or mild dementia due to Alzheimer disease who are being considered for an FDA-approved amyloid beta plaque-targeting therapy	Interventions of interest are: • Selecting patients for treatment with amyloid beta plaque-targeting therapy based on amyloid beta imaging with positron emission tomography in addition to clinical diagnosis	Comparators of interest are: • Selecting patients for treatment with amyloid beta plaque-targeting therapy based on clinical diagnosis without amyloid beta imaging	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life • Overall survival • Disease-specific survival
Individuals: • With mild cognitive impairment or mild dementia due to Alzheimer disease who are being treated with amyloid beta plaque-targeting therapy and are being evaluated for continuation of therapy	Interventions of interest are: • Continuation or discontinuation of therapy based on amyloid beta imaging with positron emission tomography in addition to assessment of cognitive and functional response to therapy	Comparators of interest are: • Continuation or discontinuation of therapy based on assessment of cognitive and functional response to therapy without amyloid beta imaging with positron emission tomography	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life • Overall survival • Disease-specific survival
Individuals: • With mild cognitive impairment to aid in prognosis	Interventions of interest are: • Tau imaging with positron emission tomography to predict conversion to Alzheimer disease	Comparators of interest are: • Clinical diagnosis alone • Postmortem histopathology	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life
Individuals: • With dementia to aid in diagnosis	Interventions of interest are: • Tau imaging with positron emission tomography as an adjunct to clinical diagnosis	Comparators of interest are: • Clinical diagnosis alone • Postmortem histopathology	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Functional outcomes • Health status measures

Populations	Interventions	Comparators	Outcomes
			• Quality of life
Individuals: • With mild cognitive impairment or mild dementia due to Alzheimer disease who are being considered for an FDA-approved amyloid beta plaque-targeting therapy	Interventions of interest are: • Selecting patients for treatment with amyloid beta plaque-targeting therapy based on tau imaging with positron emission tomography in addition to clinical diagnosis	Comparators of interest are: Selecting patients for treatment with amyloid beta plaque-targeting therapy based on clinical diagnosis without amyloid beta imaging	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life • Overall survival • Disease-specific survival
Individuals: • With suspected Alzheimer disease	Interventions of interest are: • Fluorine 18 fluorodeoxyglucose positron emission tomography to diagnose Alzheimer disease	Comparators of interest are: • Clinical diagnosis without fluorine 18 fluorodeoxyglucose positron emission tomography	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life

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.

One radioactive tracer (flortaucipir F18) that binds to aggregated tau protein and can be detected in vivo with PET has been approved by the FDA for tau imaging in patients with cognitive impairment who are being evaluated for AD 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.

OBJECTIVE

The objective of this evidence review is to evaluate whether imaging with PET and FDG-PET, as an adjunct to clinical diagnosis, and whether imaging with PET in individuals who are being considered for, or being treated with, amyloid beta plaque-targeting therapy, improve the net health outcome in individuals with mild cognitive impairment or suspected Alzheimer disease.

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 6.5 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 13.8 million by 2060. [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,]

There is evidence of healthcare disparity in AD. Studies have shown that Black Americans are 1.5 to 2 times more likely than White Americans to develop AD; however, in research studies, Black participants were 35% less likely to be diagnosed with AD or similar dementias.[4,] Similarly, recent evidence indicates gender disparities as well, with females with AD 1.7 times more likely to receive treatment for dementia compared with males.[5,]

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, tau pathology, 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 amyloid beta plaques may also be present in individuals without dementia, patients with mild or subjective cognitive impairment who may or may not progress to dementia, and patients with other types of dementia. Conversely, they may be absent in a substantial proportion of patients with clinical features of AD.[6,7,8,]

The other defining pathologic hallmark of AD is tau neurofibrillary tangles (NFTs). Postmortem studies have found that NFTs more directly correlate to the severity of dementia and neurodegeneration compared to amyloid beta plaques.[9,]

18-F fluorodeoxyglucose PET (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).[10,]

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).[11,] Non-pharmacologic treatments include physical activity,[12,13,] 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).[14,]

U.S. Food and Drug Administration (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.[14,15,]

In January 2023, lecanemab (Leqembi®; Eisai) was approved by the FDA for the treatment of AD under accelerated approval, which was converted to traditional approval in July 2023. In July 2024, donanemab (Kisunla, Eli Lilly) was approved by the FDA via a traditional approval for the treatment of AD in patients with mild cognitive impairment or mild dementia stage of disease. The labeled indication for both lecanemab and donanemab is for the treatment of AD in patients with mild cognitive impairment or mild dementia stage of disease. The labels indicates that the presence of amyloid beta pathology should be confirmed prior to initiating treatment.

REGULATORY STATUS

Radiopharmaceuticals for Positron Emission Tomography Imaging

The following PET radiopharmaceuticals have been evaluated and approved as drugs by the FDA for use as diagnostic imaging agents in individuals with cognitive impairment (Table 1).

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

Agent	Trade Name	Manufacturer	NDA	Approved	Indication for Use
florbetapir F18	Amyvid	Avid Radiopharmaceuticals (subsidiary of Eli Lilly)	202008	2012	• PET imaging of the brain to estimate ***β-amyloid*** neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. • A negative Amyvid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological 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. • A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder. • Amyvid is an adjunct to other diagnostic evaluations. • Safety and effectiveness of Amyvid have not been established for predicting the development of dementia or other neurologic condition or monitoring responses to therapies.
flutemetamol F18	Vizamyl	GE Healthcare	203137	2013	• PET imaging of the brain to estimate ***β-amyloid*** neuritic plaque density in adult patients with cognitive impairment who are being

Agent	Trade Name	Manufacturer	NDA	Approved	Indication for Use
					evaluated for AD or other causes of cognitive decline. • A negative Vizamyl scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological 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. • A positive Vizamyl scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions, as well as older people with normal cognition. • A positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder. • Vizamyl is an adjunct to other diagnostic evaluations. • Safety and effectiveness of Vizamyl have not been established for predicting the development of dementia or other neurological condition or monitoring responses to therapies.
florbetaben F18	Neuraceq	Piramal Life Sciences	204677	2014	• PET imaging of the brain to estimate ***β-amyloid*** neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. • A negative Neuraceq scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of

Agent	Trade Name	Manufacturer	NDA	Approved	Indication for Use
					image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. • A positive Neuraceq scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. A positive Neuraceq scan does not establish the diagnosis of AD or any other cognitive disorder. • Neuraceq is an adjunct to other diagnostic evaluations. • Safety and effectiveness of Neuraceq have not been established for predicting the development of dementia or other neurologic conditions or monitoring responses to therapies.
flortaucipir F18	Tauvid	Eli Lilly and Company	212123	2020	• PET imaging of the brain to estimate the density and distribution of aggregated ***tau*** neurofibrillary tangles (NFTs) in adult patients with cognitive impairment who are being evaluated for AD. • Not indicated for use in the evaluation of patients for chronic traumatic encephalopathy (CTE).

AD: Alzheimer disease; FDA: U.S. Food and Drug Administration; NDA: new drug application PET: positron emission tomography.

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.

POLICY

A. 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 **medically necessary** (see Policy Guidelines).

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

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

D. 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 **experimental / investigational**.

E. Tau imaging with PET to predict conversion to Alzheimer disease is considered **experimental / investigational**.

F. Tau imaging with PET as an adjunct to clinical diagnosis in individuals with dementia is considered **experimental / investigational**.

G. Tau 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 **experimental / investigational**.

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

I. All other uses of amyloid beta imaging with PET are considered **experimental / investigational**.

POLICY GUIDELINES

A. The labels for FDA-approved, amyloid beta targeting therapies, LEQEMBI® (lecanemab) and Kisunla™ (donanemab), state that the presence of amyloid beta pathology should be confirmed prior to initiating treatment. In the pivotal randomized controlled trial for lecanemab (Clarity AD), the protocol states that the eligibility criteria related to amyloid beta pathology required 'confirmed amyloid pathology indicated by either 1) positive amyloid load confirmed by amyloid PET assessment, or 2) CSF assessment of t-tau / Aβ[1-42].' The protocol for the pivotal randomized trial for donanemab (TRAILBLAZER-ALZ 2) states that the eligibility criteria related to amyloid beta pathology required that the patient must 'meet flortaucipir F18 scan (central read) criteria'.

B. **Lecanemab Monitoring**
The product label of lecanemab recommends that a baseline brain MRI within 1 year must be done prior to initiating treatment due to the risk of ARIA. Subsequently, MRI should be repeated prior to the fifth, seventh, and fourteenth infusions. Follow recommendations for

dosing interruptions in individuals with ARIA as specified in the US FDA-approved prescribing label.

C. **Donanemab Monitoring**
The product label of donanemab recommends obtaining a recent brain MRI prior to initiating treatment. MRI should be repeated before the second, third, fourth and seventh infusions to monitor for ARIA. Follow recommendations for dosing interruptions in individuals with ARIA as specified in the US FDA-approved prescribing label.

The label suggests stopping dosing with donanemab based on reduction of amyloid plaques to minimal levels on amyloid PET imaging.

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through May 23, 2024.

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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 individuals who have mild cognitive impairment (MCI) is to determine the amyloid beta burden and the likelihood of developing Alzheimer disease (AD).

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

Populations
The relevant population of interest is individuals with MCI.

Mild cognitive impairment is a syndrome in which persons experience memory loss (amnestic MCI) or loss of thinking skills other than memory loss (non-amnestic MCI), to a greater extent than expected for age, but without impairment of day-to-day functioning. Individuals with MCI are at increased risk of developing dementia (whether from AD or another etiology), but many do not progress to dementia, and some get better.[16,]

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 (e.g., polysomnography) to evaluate these other potential causes of cognitive impairment.

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

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

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

Ruan et al (2023) conducted a systematic review with meta-analyses of amyloid beta PET for AD, including early prediction of MCI converting to AD.[17,] The pooled sensitivities and specificities were calculated using a Bayesian random-effects model. The review included 48 studies with 5967 participants overall, of which 8 studies reported performance characteristics for the conversion of MCI to AD.

Martinez et al (2017) 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.

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
Ruan et al (2023)[17,]	Through Jan 2022	Studies included participants with AD, MCI, non- AD dementia, and normal controls. Median	11C-PIB PET[1] 18F PET with florbetapir 18F PET with florbetab	48 (N=5967) overall 8 studies on conversion of	Retrospective or prospective studies (excluding case series) with n>5	6 studies had a reference standard of brain autopsy or brain tissue biopsy; 42 studies had a	Varied from 1 month to 19 years	Sensitivity, 0.84 (95% CI, 0.74 to 0.92) Specificity, 0.62 (95% CI, 0.56 to 0.68)	High-risk bias in patient selection (case-control studies), approximately 50% High-risk

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
		age range was 60 to 79 years.	en 18F PET with flutemetamol	MCI to AD		reference standard of comprehensive clinical diagnostic criteria				bias in index tests (unblinded, threshold set after examination), approximately 20% Uncertain risk bias in reference standards, approximately 40% Uncertain risk bias in flow and timing, approximately 20%
								By Visual Assessment	By SUVR	
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	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	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

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
		the Petersen criteria or revised Petersen criteria.			a reference standard					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 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	1.6 years and 3 years	*Follow-up from 2 to <4 years:* Sensitivity 67% (95% CI, 30% to	*Follow-up from 1 to <2 years (n=401, 1 study):*	Uncertainty about the clinical diagnosis of AD; lack of information regarding

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
								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%)	Sensitivity 87% (95% CI, 76% to 94%) Specificity of 51% (95% CI, 45% to 56%)	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.
[1]11C-PIB is the prototype for many 18F compounds, including florbetapir, florbetaben, and flutemetamol.

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, more effective therapy, or avoid unnecessary therapy or 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). Studies that describe management changes due to changes in diagnosis, diagnostic certainty, or medications are not included unless they also include assessment of clinical outcomes to determine whether management changes led to improvements in outcomes.

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 3).[27,] Changes in diagnosis and patient management are shown in Table 4. 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 5 and 6). 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 3. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	***Comparator***
Pontecorvo et al (2017)[27,]	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 4. Summary of Key RCT Results

Study	Change in Diagnosis	Change in Patient Management	Cognitive Performance	Function	Quality of Life
Pontecorvo et al (2017)[27,]					
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 5 and 6.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Pontecorvo et al (2017)[27,]	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 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Pontecorvo et al (2017)[27,]		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. 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 individuals 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 therapies, aducanumab, lecanemab and donanemab. 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 use of amyloid beta PET imaging to select patients for targeting therapy is discussed in the following section.

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

Populations
The population of interest is individuals 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 (e.g., 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

Systematic Reviews

The Ruan et al (2023) systematic review and meta-analysis described in the previous section also included an estimate of performance characteristics of amyloid beta PET for differentiating AD from normal controls. Ruan Study characteristics and limitations are available in the previous section (see Table 2). Twenty-nine studies were included in the analysis of AD versus normal controls. The pooled sensitivity was 0.91 (95% CI, 0.88 to 0.93) and the pooled specificity was 0.81 (95% CI, 0.77 to 0.86).[

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.[28,29,30,31,32,33,34,] In some studies, autopsy results were available to confirm the accuracy of the tracers to determine amyloid beta levels (Table 7). 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 7. 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)[31,] 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)[32,]; Salloway et al (2017)[33,] 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)[28,29,] 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.[35,] 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, more effective therapy, or avoid unnecessary therapy or 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. Studies that describe management changes due to changes in diagnosis, diagnostic certainty, or medications are not included unless they also include assessment of clinical outcomes to determine whether management changes led to improvements in outcomes.

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 3).[27,] Changes in diagnosis and patient management are shown in Table 4. 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 5 and 6).

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 (i.e., improvement in net health outcomes resulting from testing) is lacking. The single RCT identified had insufficient power to determine the effect of amyloid beta imaging on health outcomes (i.e., 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.

Three monoclonal antibodies have been approved by the FDA as targeted therapy to reduce amyloid beta plaques. In June 2021, aducanumab (Aduhelm®; Biogen) was approved by the FDA under accelerated approval based on reduction in amyloid beta plaques. In January 2024, Biogen announced that the company was discontinuing the development and commercialization of aducanumab.

In January 2023, lecanemab (Leqembi®; Eisai), was approved by the FDA for the treatment of AD under accelerated approval, which was converted to traditional approval in July 2023. The labeled indication is for the treatment of AD in patients with mild cognitive impairment or mild dementia stage of disease.

A third monoclonal antibody that targets amyloid beta, donanemab, was approved by FDA in July 2024.[36,]

The labels for both lecanemab and donanemab indicate that the presence of amyloid beta pathology should be confirmed prior to initiating 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.[37,] The National Institute on Aging and the Alzheimer's Association have created a "numeric clinical staging scheme" (Table 8) 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. 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.[38,]

Table 8. 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 AD**	**Mild Dementia**	**Moderate Dementia**	**Severe Dementia**
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)[39,]

[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 (e.g., 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 (e.g., a measure of cognition) and a global clinical measure (e.g., a clinician's judgement of change) or a functional measure (e.g., activities of daily living).[38,] 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.[40,] 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.[41,]

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.

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 studies conducted as part of the clinical development program for lecanemab (Table 9). The phase 3 studies were multicenter, global, randomized, double-blind, placebo-controlled studies with the primary objective of efficacy and safety. In all studies, the diagnosis of AD was confirmed by presence of amyloid pathology measured by 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).[42,43,]

Results for the pivotal trial of donanemab (NCT04437511) have also been published.[36,]

This section briefly summarizes these studies..

Table 9. Summary of the Phase 3 RCTs for Aducanumab and Lecanemab

Trial	NCT		Description	N	Design	Status
Clarity AD (Study 301)	NCT03887455		Confirmatory study in early AD (i.e., MCI due to AD and mild AD dementia).	1795	DB RCT	Completed and published
AHEAD 3-45 Study	NCT04468659		Assess if lecanemab can slow accumulation of amyloid, tau, and prevent cognitive decline in cognitively unimpaired individuals (i.e., preclinical AD): intermediate amyloid (20 to 40 centiloids) and elevated amyloid (>40 centiloids)	1400	DB RCT	Ongoing

AD: Alzheimer disease; DB: double-blind; LTE: long-term extension; RCT: randomized controlled trial.

Lecanemab

Lecanemab has been evaluated in 2 double-blind RCTs (Study 201 and Study 301/Clarity AD) with samples sizes of 390 and 1795. The trials included individuals with MCI due to AD or mild AD dementia with confirmed amyloid beta pathology. In Clarity AD, the protocol states that amyloid beta pathology was confirmed by either 1) positive amyloid load confirmed by amyloid PET assessment, or 2) CSF assessment of t-tau / Aβ[1-42].

Study 201 was a phase 2, dose-finding, double-blind, placebo-controlled trial. The trial included an 18-month placebo-controlled treatment period, and a safety follow-up period of 3 months after the final dose. For the placebo-controlled period, patients were randomized to placebo or 1 of 5 lecanemab dosing regimens, including the FDA approved dosing regimen of 10 mg/kg biweekly. The primary endpoint was change from baseline on a weighted composite score called Alzheimer's Disease Composite Score (ADCOMS) consisting of selected items from the CDR-SB, Mini-Mental State Examination (MMSE), and Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale (ADAS-Cog 13) at week 53.

Study 301 (Clarity AD, study 2 in the prescribing label) was a multicenter, randomized, double-blind, placebo-controlled trial comparing 10 mg/kg biweekly lecanemab (n=898) to placebo (n=897). The study included an 18-month (78-week) placebo-controlled period and a safety follow-up period of 3 months after the final dose. Participants met criteria for either MCI due to AD or mild AD dementia and were required to have evidence of brain Aβ pathology by either visual read of a PET scan or CSF assessment of t-tau/Aβ1-42. Participants had a baseline MMSE score of 22 to 30 and a CDR global score of 0.5 or 1.0 with a Memory Box score of 0.5 or greater. The primary efficacy endpoint was the change from baseline in CDR-SB at 18 months.

Both trials reported an approximately 27% statistically significantly slower rate of decline for the primary cognitive and functional outcome (ADCOMS for Study 201; CDR-SB for Study 301) for lecanemab versus placebo.[43,]

ARIA was observed in 21% (191/898) of individuals treated with lecanemab compared to 9% (84/897) of individuals who received placebo. Symptomatic ARIA occurred in 3% (29/898) of individuals treated with lecanemab. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of individuals treated with lecanemab.[44,45,43,]

Lecanemab received traditional FDA approval based on results of these RCTs and the label for lecanemab states that the presence of amyloid beta pathology should be confirmed prior to initiating treatment.[45,]

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 RCTs. The Clarity AD trial demonstrated a 27% (difference, -0.45; 95% Cl, −0.67 to −0.23) statistically significantly slower rate of decline on the CDR-SB for lecanemab versus placebo. The differences in rate of change over time consistently favored lecanemab across cognitive, functional, quality of life, and caregiver burden outcomes. ARIA was observed in 21% of individuals treated with lecanemab; 3% of individuals treated with lecanemab experienced symptomatic ARIA. Lecanemab received traditional FDA approval with a label indicating that the

presence of amyloid beta pathology should be confirmed prior to initiating treatment. Donanemab has also received traditional FDA approval with a label indicating that the presence of amyloid beta pathology should be confirmed prior to initiating treatment.

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 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

The lecanemab product label recommends monitoring for ARIAs using magnetic resonance imaging (MRI), but does not address monitoring amyloid beta burden during treatment using PET to inform decisions regarding continuation of treatment.

In the pivotal TRAILBLAZER-ALZ 2 (NCT04437511) phase 3 trial of the anti-amyloid monoclonal antibody, donanemab, randomized participants received either donanemab or placebo, administered intravenously every 4 weeks for 72 weeks or until amyloid clearance criteria were met (amyloid plaque level, measured at 24 weeks and 52 weeks, less than 11 Centiloids on any single PET scan or less than 25 but greater than or equal to 11 Centiloids on 2 consecutive PET scans). Thirty percent of participants in the donanemab group met amyloid clearance criteria at 24 weeks and 76% met criteria at 76 weeks and therefore could stop treatment with donanemab. Cognitive outcomes for the participants who discontinued treatment after meeting clearance criteria are not available.[36,]

Section Summary: Amyloid Beta Imaging With Positron Emission Tomography to Evaluate Patients Receiving Targeting Therapy for Continuation of Treatment
The only evidence identified on using amyloid beta PET imaging to determine whether to continue amyloid targeting therapy is related to donanemab. Cognitive outcomes for the participants who discontinued treatment after meeting clearance criteria are not available.

TAU 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 tau imaging with PET in individuals who have MCI is to determine the presence of tau pathology and the likelihood of developing AD.

Tau is part of the family of microtubule-binding proteins that are especially common in neurons. Neurofibrillary tangles (NFTs) are aggregates of hyperphosphorylated tau protein that are one of the neuropathological hallmarks of AD.[46,] At autopsy, the NFT burden in AD is defined by Braak stages. Braak stage is based on the anatomical localization of NFTs: Stage 1, transentorhinal cortex; Stage 2, entorhinal cortex and hippocampus; Stage 3, inferior temporal neocortex; Stages 4 and 5, association cortices; Stage 6, primary sensory cortices.[47,] Braak staging is part of the criterion standard diagnosis for AD at autopsy but is primarily a histopathological construct.

Tau NFT locations can be imaged with a PET scan. Several tau PET imaging tracers are in development. One tracer (flortaucipir F18) has been approved by the FDA. Tau PET imaging has been proposed as a way to approximate the Braak staging system in living humans in order to model the severity of clinical impairment from presymptomatic to clinical dementia.

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

Populations
The relevant population of interest is individuals with MCI.
Mild cognitive impairment is a syndrome in which persons experience memory loss (amnestic MCI) or loss of thinking skills other than memory loss (non-amnestic MCI), to a greater extent than expected for age, but without impairment of day-to-day functioning. Individuals with MCI are at increased risk of developing dementia (whether from AD or another etiology), but many do not progress to dementia, and some get better. [16,]

Interventions
The intervention of interest is tau imaging using a commercially available PET tracer (flortaucipir F18).

The label for the FDA-approved flortaucipir F18 tracer, TAUVID™, states that the indication is to 'estimate the density and distribution of aggregated tau NFTs in adult patients with cognitive impairment who are being evaluated for AD.'[48,]

Defining tau positivity requires evaluation of both the quantity of tracer retention and its location. The flortaucipir F18 label describes the visual interpretation of the images. It does not provide guidance on quantitative analysis with SUVRs (standardized uptake value ratios).

Weigand et al (2022) published a systematic review of tau PET thresholding methods for flortaucipir tau PET tracers. They found notable variability in tau PET SUVR cutpoints across published studies with a total of 82 SUVR cutpoints reported across 23 studies ranging from 1.13 to 2.79. The mean cut-point was 1.33 with a standard deviation of 0.21.[49,]

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 tau 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 tau pathology 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; a false-negative test may lead to additional unnecessary tests 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 tau 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 tau imaging 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
No studies were identified that report the sensitivity and specificity of flortaucipir F18 tau PET for predicting conversion of MCI to AD.

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, more effective therapy, or avoid unnecessary therapy or 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. Studies that describe management changes due to changes in diagnosis, diagnostic certainty, or medications are not included unless they also include assessment of clinical outcomes to determine whether management changes led to improvements in outcomes.

There is no direct evidence that using flortaucipir F18 tau PET to predict conversion of MCI to AD improves clinical outcomes.

Section Summary: Tau Imaging With Positron Emission Tomography to Predict Conversion to Alzheimer Disease in Patients with Mild Cognitive Impairment
One proposed use for tau imaging is to determine which patients with MCI have a likelihood of converting to AD. No studies were identified that report the sensitivity and specificity of flortaucipir F18 tau PET for predicting conversion of MCI to AD. Direct evidence on clinical utility is not available.

TAU IMAGING WITH POSITRON EMISSION TOMOGRAPHY AS AN ADJUNCT TO CLINICAL ASSESSMENT TO DIAGNOSE ALZHEIMER DISEASE IN PATIENTS WITH DEMENTIA

Clinical Context and Test Purpose

Tauopathies are neurodegenerative disorders defined by abnormal tau protein deposition in the nervous system. Tauopathies can present with a range of clinical phenotypes related to the site and spread of involvement including cognitive or behavioral symptoms, movement symptoms, language symptoms, and non-specific amnestic symptoms. Tauopathies can be classified pathologically based on the predominant tau isoforms deposited in the nervous system and can be considered either the primary or a co-pathology. Tauopathies include those with a strong association with the underlying tau pathology (e.g., Richardson syndrome, corticobasal syndrome, behavioral variant frontotemporal dementia) and those with a weak association with an underlying tau pathology (e.g., Parkinsonian syndrome, primary lateral sclerosis).[46,] The clinical presentations can guide diagnosis but the large overlap in clinical phenotypes makes it challenging to differentiate tauopathies accurately. One proposed use of tau PET imaging in patients with dementia is to aid in differential diagnosis between AD and non-AD causes of cognitive impairment in order to guide appropriate treatment and/or further testing.

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

Populations

The population of interest is individuals with dementia.

Interventions

The intervention of interest is tau imaging using a commercially available PET tracer (flortaucipir F18).

The label for the FDA-approved flortaucipir F18 tracer, TAUVID™, states that the indication is to 'estimate the density and distribution of aggregated tau NFTs in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease.' The label includes a warning that users should 'Consider additional evaluation to confirm the absence of AD pathology in patients with a negative TAUVID scan.'[48,] This tracer has not been approved for measuring non-AD tauopathies such as frontotemporal lobar degeneration.

Defining tau positivity requires evaluation of both the quantity of tracer retention and its location. The flortaucipir F18 label describes the visual interpretation of the images. It does not provide guidance on quantitative analysis with SUVRs.

Weigand et al (2022) published a systematic review of tau PET thresholding methods for flortaucipir tau PET tracers. They found notable variability in tau PET SUVR cutpoints across published studies with a total of 82 SUVR cutpoints reported across 23 studies ranging from 1.13 to 2.79. The mean cut-point was 1.33 with a standard deviation of 0.21.[49,]

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 (e.g., 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 tau 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
Studies describing the sensitivity and specificity of flortaucipir F18 tau PET are described in the following paragraphs and Table 10.

The clinical validity of tau PET with the FDA-approved tracer flortaucipir F18 for diagnosing AD was evaluated in Study 1 (NCT02516046) described in the product label and Fleisher et al (2020).[48,50,] Study 1 enrolled 156 terminally ill individuals who were participating in a postmortem brain donation program. The participants had a range of cognitive status from normal to dementia, including AD and non-AD dementia. Reader interpretation of the PET scan was

compared to tau pathology at autopsy in 64 of the participants. PET imaging was interpreted by 5 independent readers who were blinded to clinical information; readers visually interpreted imaging as positive or negative. Tau pathology at autopsy was determined by independent pathologists who evaluated the density and distribution of NFTs in the postmortem brain. The mean age was 83 years (range, 55 to 100), 34 (53%) patients were female, 49 (77%) had dementia, 1 (2%) had mild cognitive impairment, and 14 (22%) had no cognitive impairment. Sensitivity and specificity were provided for each reader separately. A 'majority read' analysis was also performed. The majority read was defined as either a negative, moderate, or advanced AD pattern based on 3 of 5 readers. The performance of the tau PET for the 5 readers for sensitivity ranged from 92% (95% CI, 80% to 97%) to 100% (95% CI, 91% to 100%). Specificity ranged from 52% (95% CI, 34% to 70%) to 92% (95% CI, 75% to 98%). The sensitivity for the majority read analysis was 89% (95% CI, 77% to 95%) with specificity of 86% (95% CI, 71% to 94%).[48,50,]

Ossenkoppele, et al (2018) reported the performance of 18F flortaucipir tau PET for differentiating AD from other neurodegenerative disorders.[34,] The study was a cross-sectional study with 719 participants recruited from 3 dementia centers in South Korea, Sweden, and the United States conducted between June 2014 and November 2017. The participants included 160 cognitively normal controls, 126 patients with MCI, 179 patients with AD, and 254 patients with non-AD neurodegenerative disorders. Tau positivity was determined by SUVR in 5 predefined regions of interest. Cutpoints for positivity were created using 2 methods 1) mean plus 2 standard deviations observed in controls, and 2) Youden Index. The reference standard was clinical diagnosis determined at the specialized memory centers. The mean age was 69 years and 48% of the participants were male. For distinguishing AD dementia from non-AD neurodegenerative disorders, sensitivity of tau positivity in the medial-basal and lateral temporal cortex was 90% (95% CI, 85% to 94%); specificity was 91% (95% CI, 86% to 94%) using the cutpoint based on controls (SUVR, 1.34). The sensitivity was 97% (95% CI, 92% to 99%) with 88% (95% CI, 82% to 92%) specificity using the Youden Index–derived cutpoint (SUVR, 1.27).[34,]

Dang et al (2022) reported on the performance of tau flortaucipir 18F PET to distinguish individuals with AD from normal controls.[51,] The study enrolled 83 AD patients and 38 cognitively normal controls who were participating in an ongoing community-based cohort study in China. Selection criteria were not described. The mean age was 64 years; 55% were male. The reference standard was clinical diagnosis. Criteria used for tau PET positivity were unclear. The sensitivity and specificity for distinguishing AD from normal controls were 0.64 and 0.96, respectively. Confidence intervals were not given.[51,]

Table 10. Performance characteristics of 18F flortaucipir tau PET for diagnosing Alzheimer disease

Study	Dates of study conduct	Countries	Populations	N	Study Design	Reference Standard	Visual vs. Quantitative read	Performance
Prescribing label and Fleisher	2015 to 2018	US and Australia	Individuals with a terminal illness; age >50 yrs; life	64	Prospective	Determined by independent	Visual, 5 readers	Across 5 readers-Sensitivity, ranged

Study	Dates of study conduct	Countries	Populations	N	Study Design	Reference Standard	Visual vs. Quantitative read	Performance
(2020) [48,50],			expectancy <6 mths Mean age, 83 yrs; 53% women; 97% White			pathologists who evaluated the density and distribution of NFTs in the postmortem brain		from 92% (95% CI, 80-97) to 100% (95% CI, 91-100) Specificity, ranged from 52% (95% CI, 34-70) to 92% (95% CI, 75-98)
Ossenkoppele (2018) [34],	2014 to 2017	South Korea, Sweden, US	Individuals with a range of neurodegenerative diseases Mean age, 69 yrs; 48% men	719	Cross-sectional, convenience sample	Clinical diagnosis determined at the specialized memory centers	Quantitative, SUVR cutpoint at 1.34 for medial-basal and lateral temporal cortex	Sensitivity, 90% (95% CI, 85-94) Specificity, 91% (95% CI, 86-94)
Dang (2022)[51],	NR	China	Participants from a community based study Mean age, 64 yrs; 55% men	121 (83 with AD and 38 controls)	Unclear; sampled from cohort study, selection not described	Clinical diagnosis	Unclear	Sensitivity, 64% (95% CI, NR) Specificity, 96% (95% CI, NR)

AD: Alzheimer disease; CI: confidence interval; NR: not reported; SUVR: standardized uptake value ratios.

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, more effective therapy, or avoid unnecessary therapy or 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. Studies that describe management changes due to

changes in diagnosis, diagnostic certainty or medications are not included unless they also include assessment of clinical outcomes to determine whether management changes led to improvements in outcomes.

There is no direct evidence that using flortaucipir F18 tau PET as an adjunct to clinical assessment for diagnosis of AD improves clinical outcomes.

Section Summary: Tau Imaging With Positron Emission Tomography as an Adjunct to Clinical Assessment to Diagnose Alzheimer Disease in Patients with Dementia
Tau PET is proposed as an adjunct to clinical assessment to diagnose AD in patients with dementia. Tau neurofibrillary tangles are one of several markers of AD on histopathology but are necessary for a diagnosis of AD. A negative tau PET scan would, in theory, be associated with a lower likelihood of AD. One study (N=64) was identified that used a reference standard of autopsy-confirmed diagnosis and reported sensitivities ranging from 92% to 100% with specificities ranging from 52% to 92% across 5 readers. In the largest study (N=719), the sensitivity for distinguishing AD dementia from non-AD neurodegenerative disorders was 90% or 97% depending on how the cutpoint was defined. Specificity was 91% or 88% depending on cutpoint. There is not yet a consensus on the appropriate regions of the brain and cutpoints for defining tau PET positivity for quantitative analysis. Direct evidence on clinical utility (i.e., improvement in net health outcomes resulting from testing) is lacking.

TAU IMAGING WITH POSITRON EMISSION TOMOGRAPHY TO SELECT PATIENTS FOR TARGETING THERAPY

Clinical Context and Test Purpose
The purpose of tau imaging with PET in individuals with MCI or mild dementia due to AD is to guide a decision about the initiation of targeting therapy.

For tau-targeting therapy, the tau PET test is intended to exclude individuals with clinically diagnosed MCI/AD that do not have tau neurobiology and to select for treatment those tau positive individuals that are potentially able to benefit from treatment. There are several candidate tau-targeting therapies in development, but none have regulatory approval.

For amyloid-beta targeting therapy, the tau PET test is intended to identify individuals early in the AD disease process when it is thought that targeting beta amyloid might have the most benefit.

Three monoclonal antibodies have been approved by the FDA as targeted therapy to reduce amyloid beta plaques. The pivotal trials for aducanemab and lecanemab therapies did not include testing for tau pathology as an entry criterion. The entry criteria for the pivotal trial for donanemab included confirmation of early symptomatic AD with both amyloid and tau pathology.[36,]However, the label for donanemab does not include requirement of tau PET imaging before initiation of 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 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.[37,] The National Institute on Aging and the Alzheimer's Association's "numeric clinical staging scheme" was discussed in the previous section on amyloid beta PET for targeting therapy, see Table 8.

Interventions
The intervention of interest is tau imaging using a commercially available PET tracer (flortaucipir F18).

In the pivotal TRAILBLAZER-ALZ 2 trial for donanemab, individuals with no or very low tau were excluded because 'their expected rate of disease progression would not allow for reliable measurement of clinical decline or of study treatment effects within an 18-month study duration.'[36,] TRAILBLAZER-ALZ 2 included individuals who were categorized as low/medium tau or high tau, defined as follows.

Low/medium tau:
- 1.10 ≤ SUVr ≤1.46, with a topographic deposition pattern consistent with moderate AD, or
- SUVr ≤1.46, with a topographic deposition pattern consistent with advanced AD

High tau:
- SUVr >1.46, with a topographic deposition pattern consistent with either moderate or advanced AD.[36,]

Comparators
The comparator of interest is standard clinical management without tau 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 (e.g., 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.

Tau PET is intended to identify individuals with the required tau pathology that are targeted by the therapy (tau-targeting therapy) or individuals early in the disease process when targeting amyloid beta is thought to be more effective (amyloid beta-targeting therapy). 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 (e.g., a measure of cognition) and a global clinical measure (e.g., a clinician's judgement of change) or a functional measure (e.g., activities of daily living).[38,] 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 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.[40]

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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 tau PET in patients with suspected AD is addressed above in this review.

Clinical Utility

There are no FDA-approved tau-targeting therapies. Evidence about the clinical utility of tau PET imaging to select patients for treatment with amyloid beta targeting-therapy is available from studies conducted as part of the clinical development program for donanemab (Table 11). This section briefly summarizes the study.

Table 11. Summary of the Phase 3 RCTs for Donanemab

Trial	NCT	Description	N	Design	Status
TRAILBLAZER-ALZ 2	NCT04437511	Assess efficacy and adverse events of donanemab in early symptomatic AD	1736	DB RCT	Completed and published

AD: Alzheimer disease; DB: double-blind; LTE: long-term extension; RCT: randomized controlled trial.

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

For individuals with MCI or mild dementia due to AD who are being considered for an FDA-approved targeting therapy, the evidence includes one RCT. TRAILBLAZER-ALZ 2 was a randomized, double-blind, placebo-controlled study that enrolled patients with early AD and evaluated the efficacy and safety of donanemab, an amyloid beta-targeting therapy. Confirmation of tau pathology using tau PET was required as an entry criteria. However, the label for donanemab does not include requirement of tau PET imaging before initiation of treatment.

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 individuals with suspected AD is to confirm a diagnosis of AD.

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

Populations

The population of interest is individuals 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 neuropsychological examinations, and interviews with informants (e.g., 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 12 and 13, and are briefly described below.

Table 12. Characteristics of Systematic Reviews on FDG-PET for Diagnosing AD and Dementia

Study	Dates	Studies	N (Range)	Design	Outcomes
Zhu et al (2022)[52,]	Up to 2020	16	NR	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Smailagic et al (2015)[53,]	1999-2013	16	697 (19-94)	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Davison et al (2014)[54,]	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)[55,]	1990-2010	119	NR	OBS	Diagnostic accuracy for diagnosis of AD, differential diagnosis in dementia
Yuan et al (2009)[56,]	2001-2005	6	280 (17-128)	OBS	Diagnostic accuracy for predicting conversion from MCI to AD
Matchar et al (2001)[57,]	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).[52,] 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.[53,] 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. 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.[54,] 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.[55,] 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.

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.[56,] 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. 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 (e.g., 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.[57,] 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. 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 13. Results of Systematic Review on Use Assessing FDG-PET for AD and Dementia

Study	Studies	N	Outcomes	Estimate (95% CI)
Zhu et al (2022)[52,]	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)[53,]	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)[54,]	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)[55,]	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)[56,]	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)[57,]	15	729	Diagnostic accuracy	• Sensitivity: 88% (79% to 94%)

Study	Studies	N	Outcomes	Estimate (95% CI)
				• 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. Studies that describe management changes due to changes in diagnosis, diagnostic certainty, or medications are not included unless they also include assessment of clinical outcomes to determine whether management changes led to improvements in outcomes.

There is no direct evidence of the clinical utility of FDG-PET for diagnosing AD.

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.

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).[58,]

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.[59,] They recommended that amyloid imaging is appropriate for individuals with all of the following characteristics:

"(i) a cognitive complaint with objectively confirmed impairment; (ii) AD [Alzheimer disease] as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert; and (iii) when knowledge of the presence or absence of AD pathology is expected to increase diagnostic certainty and alter management."

Appropriate candidates include:
1. Patients with unexplained persistent or progressive MCI [mild cognitive impairment].
2. Patients satisfying core clinical criteria for possible AD, but are unusual in the clinical presentation.
3. Patients with progressive dementia and atypically early age of onset (e.g., 65 years of age or less).

Amyloid imaging is inappropriate in the following situations:
1. "Patients with core clinical criteria for probable AD with typical age of onset.
2. To determine dementia severity.
3. Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE) ε4.
4. Patients with a cognitive complaint that is unconfirmed on clinical examination.
5. In lieu of genotyping for suspected autosomal mutation carriers.
6. In asymptomatic individuals.
7. Nonmedical use (e.g., legal, insurance coverage, or employment screening)."

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).[60,]

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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	Aug 2024
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
NCT04437511[a]	Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 2)	1736	Aug 2025
NCT05508789[a]	Global Study to Investigate Safety and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 5)	1500	Apr 2027
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	Nov2027
NCT03860857	MRI and PET Biomarkers for Cognitive Decline in Older Adults	200	Dec 2027
NCT05457998	BioFINDER-Brown: Examination of Alzheimer's Disease Biomarkers	200	Jun 2028
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	Feb 2029
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.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
78608	Brain imaging, positron emission tomography (PET); metabolic evaluation
78609	Brain imaging, positron emission tomography (PET); perfusion evaluation
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)
A9586	Florbetapir F18, diagnostic, per study dose, up to 10 millicuries
Q9982	Flutemetamol F18, diagnostic, per study dose, up to 5 millicuries
Q9983	Florbetaben F18, diagnostic, per study dose, up to 8.1 millicuries

REVISIONS	
Posted 12-03-2024 Effective 01-02-2025	Policy added to the bcbsks.com web site.

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