**MP 6.01.55**  
Beta-Amyloid Imaging with Positron Emission Tomography for Alzheimer Disease

**Related Policies**
- 2.04.14 Biochemical Markers of Alzheimer Disease
- 6.01.54 Dopamine Transporter Imaging with Single-Photon Emission Computed Tomography

**DISCLAIMER/INSTRUCTIONS FOR USE**
Medical Policy provides general guidance for applying Blue Cross of Idaho benefit plans (for purposes of Medical Policy, the terms “benefit plan” and “member contract” are used interchangeably). Coverage decisions must reference the member specific benefit plan document. The terms of the member specific benefit plan document may be different than the standard benefit plan upon which this Medical Policy is based. If there is a conflict between a member specific benefit plan and the Blue Cross of Idaho’s standard benefit plan, the member specific benefit plan supersedes this Medical Policy. Any person applying this Medical Policy must identify member eligibility, the member specific benefit plan, and any related policies or guidelines prior to applying this Medical Policy. Blue Cross of Idaho Medical Policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the member specific benefit plan coverage. Blue Cross of Idaho reserves the sole discretionary right to modify all its Policies and Guidelines at any time. This Medical Policy does not constitute medical advice.

**POLICY**
Beta-amyloid imaging with positron emission tomography is **investigational**.

**POLICY GUIDELINES**
None

**BENEFIT APPLICATION**

**BLUECARD/NATIONAL ACCOUNT ISSUES**
State or federal mandates (e.g., Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

**BACKGROUND**

**ALZHEIMER DISEASE**

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

Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. In a study of the clinical diagnosis of possible or probable AD at national AD centers, sensitivity was shown to range from 83% to 87%, with specificity ranging from 54%.
to 44%, depending on the criteria used to establish AD at autopsy.²

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

### Table 1. Diagnosis of Alzheimer Disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Core Clinical Criteria⁵</th>
<th>Typical Course or Presentation</th>
<th>Postmortem Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Probable</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Definite</td>
<td>Yes</td>
<td>May be typical or atypical</td>
<td>Yes</td>
</tr>
</tbody>
</table>

⁵Core clinical criteria: Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests. The initial and most prominent cognitive deficits may be amnestic, which is the most common syndromic presentation of Alzheimer disease dementia, or alternatively language, visuospatial, or executive dysfunction. For nonamnestic presentations, deficits in other cognitive domains should be present.

⁶A typical clinical course is defined as an insidious onset, with the initial and most prominent cognitive deficits being either amnestic or nonamnestic (language, visuospatial, or executive dysfunction) and a history of progressively worsening cognition over time.

⁷Presence of extracellular β-amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex.

Mild cognitive impairment (MCI) may be diagnosed when there is a change in cognition, but impairment is insufficient for the diagnosis of dementia.⁴ Features of MCI are evidence of impairment in one or more cognitive domains and preservation of independence in functional abilities. In some patients, MCI may be a predementia phase of AD. Patients with MCI may undergo ancillary testing (eg, neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. The annual conversion rate of MCI to AD is between 5% and 10%.⁵

### Assessment

Because clinical diagnosis can be difficult, particularly early in the course of the disease or with atypical dementia, there has been considerable interest in developing biomarkers for AD (see evidence review 2.04.14). One biomarker being evaluated is Aβ plaque density in the brain detected in vivo by positron emission tomography (PET). Aβ plaque is a requirement for the diagnosis of definite AD, but may also be present in individuals without dementia, in patients with mild or subjective cognitive impairment who may or may not progress to dementia, and in patients with other types of dementia; conversely, it may be absent in a substantial proportion of patients with clinical features of AD.⁶⁷

PET images biochemical and physiologic functions by measuring concentrations of positron-emitting chemicals in the body region of interest. Radiopharmaceuticals used for Aβ imaging may be generated in a cyclotron or nuclear generator and introduced into the body by intravenous injection. A number of carbon 11– and fluorine 18–labeled PET radiopharmaceuticals have been investigated for imaging brain Aβ.⁸
REGULATORY STATUS
Amyvid™, Vizamyl™, and Neuraceq™ (see Table 2) are approved by the U.S. Food and Drug Administration “for PET imaging of the brain to estimate Aβ neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer disease (AD) and other causes of cognitive decline.”

Table 2. Agents Approved by the U.S. Food and Drug Administration

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>NDA</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>florbetapir F18</td>
<td>Amyvid™</td>
<td>Avid Radiopharmaceuticals (subsidiary of Eli Lilly)</td>
<td>202008</td>
<td>2012</td>
</tr>
<tr>
<td>flutemetamol F18</td>
<td>Vizamyl™</td>
<td>GE Healthcare</td>
<td>203137</td>
<td>2013</td>
</tr>
<tr>
<td>florbetaben F18</td>
<td>Neuraceq™</td>
<td>Piramal Life Sciences</td>
<td>204677</td>
<td>2014</td>
</tr>
</tbody>
</table>

NDA: new drug application.

Prescribing information for all 3 agents states:

- The objective of Aβ image interpretation “is to estimate beta-amyloid neuritic plaque density in brain gray matter, not to make a clinical diagnosis.”
- A positive Aβ scan “does not establish the diagnosis of AD or other cognitive disorder.”
- A negative Aβ scan “indicates sparse to no neuritic plaques, and is inconsistent with a neuropathologic diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient’s cognitive impairment is due to AD.”
- Florbetapir, florbetaben, and flutemetamol are not intended for use in “predicting development of dementia or other neurological condition” or for “monitoring responses to therapies.”

RATIONALE
This evidence review was created in June 2012 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 2, 2019.

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

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

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

The question addressed in this evidence review is: Does Aβ PET imaging improve the net health outcome in patients with MCI?
The following PICOs were used to select literature to inform this review.

**Patients**

The population of interest includes patients with MCI.

**Interventions**

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

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

**Comparators**

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

**Outcomes**

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

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

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

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

**Study Selection Criteria**

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

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

Studies were excluded from the evaluation of the clinical validity of the Aβ test if they did not use the marketed version of the test, did not include information needed to calculate performance characteristics, did not use an appropriate reference standard or reference standard was unclear, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria.
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

**Technically Reliable**

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

**Clinically Valid**

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

Multiple studies evaluating conversion from MCI to probable AD have been reported, and some of which are described in Tables 3 and 4. The largest prospective study was conducted by Wolk et al (2018), who reported that the hazard ratio for conversion to probable AD in patients with a baseline positive Aβ PET scan was 2.51 (p less than 0.001, see Table 4), increasing to 8.45 when low hippocampal volume and poorer cognitive status was added to the model. In a retrospective cohort study of 250 patients with MCI, Jun et al (2019) reported progression to probable AD according to amyloid tertiles on PET scan conducted at baseline. Stages were defined as stage I, negative amyloid scan (global standardized uptake value ratio less than 1.11); stage II, 1.11 to less than 1.30; stage III, 1.30 to less than 1.50; and stage IV, 1.50 or higher. The rates of progression to a diagnosis of dementia by 36 months (n=71 patients) were 2.2%, 15.5%, 32.9%, and 57.1% in stage I, II, III, and IV, respectively. In multivariate analysis, hazard ratios increased as the stage increased (stage II: 4.51; p = 0.015, stage III: 7.62; p = 0.001; stage IV: 9.42; p less than 0.001). The study authors concluded that large amyloid burden could be a predictor of fast cognitive decline in patients with MCI, but that more studies with longer follow-up times, more patients, and pathologic correlation are needed to define the role of amyloid PET imaging.

**Table 3. Study Characteristics for Patients With Mild Cognitive Impairment**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Design</th>
<th>Reference Standard</th>
<th>Threshold for Positive Index Test</th>
<th>Timing of Reference and Index Tests</th>
<th>Blinding of Assessors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolk et al (2018)</td>
<td>232 patients ≥55 y with MCI and no vascular, traumatic, or inflammatory causes</td>
<td>Prospective</td>
<td>Independent clinical adjudication committee</td>
<td>Visual rating as Aβ+ (n=98)</td>
<td>Every 6 mo for 3 y</td>
<td>Yes</td>
</tr>
<tr>
<td>Ong et al (2013, 2015)</td>
<td>45 patients with MCI</td>
<td>Prospective</td>
<td>Episodic memory Z score</td>
<td>SUVR ≥1.45 (n=24)</td>
<td>4 y</td>
<td>Yes (index); No (reference)</td>
</tr>
<tr>
<td>Doraiswamy et al</td>
<td>52 patients ≥50 y with longitudinal follow-up</td>
<td>Longitudinal</td>
<td>4-point decline on</td>
<td>Visual rating as Aβ+ (n=17)</td>
<td>3 y</td>
<td>Yes</td>
</tr>
</tbody>
</table>


(2014)\textsuperscript{13} recently diagnosed MCI the ADAS or A\textbeta- (n=30)

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

**Table 4. Clinical Validity for Patients With Mild Cognitive Impairment**

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Conversion of A\textbeta+ to pAD</th>
<th>Conversion of A\textbeta- to pAD</th>
<th>HR (95% CI) p</th>
<th>Clinical Validity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolk et al (2018)\textsuperscript{16}</td>
<td>232</td>
<td>224</td>
<td>54% of 97</td>
<td>23% of 127</td>
<td>2.51 (1.57 to 3.99) p less than 0.001</td>
<td>64 69 54 77</td>
</tr>
<tr>
<td>Ong et al (2013, 2015)\textsuperscript{14,15}</td>
<td>47</td>
<td>45</td>
<td>88% of 24</td>
<td>24% of 21</td>
<td></td>
<td>81 84 88 76</td>
</tr>
<tr>
<td>Doraiswamy et al (2014)\textsuperscript{13}</td>
<td>52</td>
<td>47</td>
<td>35% of 17</td>
<td>10% of 30</td>
<td>p=0.054</td>
<td>67 71 35 90</td>
</tr>
<tr>
<td>Summary range</td>
<td></td>
<td></td>
<td>35%-88%</td>
<td>10%-24%</td>
<td>2.51</td>
<td>64-81 69-71 35-88 76-100</td>
</tr>
</tbody>
</table>

A\textbeta+: positive A\textbeta PET scan; A\textbeta-: negative A\textbeta PET scan; CI: confidence interval; HR: hazard ratio; pAD: probable Alzheimer Disease; Spec.: The purpose of the limitations tables (see Tables 5 and 6) is to display notable limitations identified in each study.

**Table 5. Relevance Limitations**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population\textsuperscript{a}</th>
<th>Intervention\textsuperscript{b}</th>
<th>Comparator\textsuperscript{c}</th>
<th>Outcomes\textsuperscript{d}</th>
<th>Duration of Follow-Up\textsuperscript{e}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolk et al (2018)\textsuperscript{16}</td>
<td>2. Used a majority rating of 5 readers instead of a single reviewer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ong et al (2013, 2015)\textsuperscript{14,15}</td>
<td>2. Used SUVR or a majority rating of 5 readers</td>
<td>3. Used the episodic memory Z score rather than full clinical evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doraiswamy et al (2014)\textsuperscript{13}</td>
<td></td>
<td>3. Used a 4-point decline on ADAS rather than full clinical evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment. ADAS: Alzheimer Disease Assessment Scale; SUVR: standardized uptake value ratio.
b-Amyloid Imaging With Positron Emission Tomography for Alzheimer Disease

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.

Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 6. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection a</th>
<th>Blinding b</th>
<th>Delivery of Test c</th>
<th>Selective Reporting d</th>
<th>Data Completeness e</th>
<th>Statistical f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolk et al (2018)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. CIs not reported</td>
</tr>
<tr>
<td>Ong et al (2013, 2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. CIs not reported</td>
</tr>
<tr>
<td>Doraiswamy et al (2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. CIs not reported</td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

CI: confidence interval; PET: positron emission tomography.

a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
b Blinding key: 1. Not blinded to results of reference or other comparator tests.
c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Section Summary: Clinically Valid

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

**Clinically Useful**

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

**Direct Evidence**

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

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

**Table 7. Summary of Key Randomized Controlled Trial Characteristics**

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pontecorvo et al (2017)</td>
<td>U.S., EU</td>
<td>60</td>
<td>2012-2015</td>
<td>618 patients</td>
<td>Active: 308 and physicians had immediate access to Aβ PET results</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-90 y with MCI (n=342) or dementia (n=276)</td>
<td>Comparator: 310 and physicians had delayed (12 mo) access to Aβ PET results</td>
</tr>
</tbody>
</table>

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

**Table 8. Summary of Key Randomized Controlled Trial Results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in Diagnosis</th>
<th>Change in Patient Management</th>
<th>Cognitive Performance</th>
<th>Function</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pontecorvo et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>602</td>
<td>599</td>
<td>560</td>
<td>560</td>
<td>560</td>
</tr>
<tr>
<td>Immediate results, %</td>
<td>32.6</td>
<td>68</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Delayed results, %</td>
<td>6.4</td>
<td>55.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Diff/OR (95% CI)</td>
<td>Diff=26.2%</td>
<td>OR=1.70 (1.22 to 2.38)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>P</td>
<td>less than 0.001</td>
<td>less than 0.002</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NNT</td>
<td>3.8</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CI: confidence interval; Diff: difference; NNT: number needed to treat; NR: not reported; OR: odds ratio.

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

### Table 9. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Duration of Follow-Upa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pontecorvo et al (2017)</td>
<td>1. Did not distinguish between patients with MCI or AD</td>
<td>1. Health outcomes were exploratory</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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.

a Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

### Table 10. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pontecorvo et al (2017)</td>
<td>1, 2. Not blinded to treatment or outcome assessment</td>
<td>6. Not intention-to-treat and number of unclear PET scans is not reported</td>
<td>3. Not powered for health outcomes</td>
<td>3. CIs and p values not reported for health outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

CI: confidence interval; PET: positron emission tomography.


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).
MP 6.01.55
β-Amyloid Imaging With Positron Emission Tomography for Alzheimer Disease

° Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
° Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Chain of Evidence

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

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

Section Summary: Clinically Useful

Direct evidence on clinical utility is limited. One RCT reported on changes in diagnosis and management but did not find evidence that health outcomes (cognition, function, quality of life) were improved by testing. A major limitation of this study is that the evaluation of health outcomes was exploratory and not sufficiently powered. No trials have been identified that reported whether changes in diagnosis are more accurate.

Dementia

Clinical Context and Test Purpose

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

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

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

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

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

Patients

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

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

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

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

Harmful outcomes resulting from a false test result: side effects of incorrect or unnecessary treatment; not receiving correct treatment or failing to undergo additional testing such as formal neuropsychological testing and functional neuroimaging studies (eg single-photon emission computed tomography, perfusion magnetic resonance imaging, or fluorine 18 fluorodeoxyglucose 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 three years to monitor progression (or lack of progression) of disease. Direct evidence of an immediate effect of therapy is observable after two months of treatment with acetylcholinesterase inhibitors or memantine.

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

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

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

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

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

**Clinically Valid**

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

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Clinical Diagnosis</th>
<th>Interval From Imaging</th>
<th>Read(s)</th>
<th>Sensitivity (95% CI or Range), %</th>
<th>Specificity (95% CI or Range), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabri et al (2015)(^{24})</td>
<td>74</td>
<td>AD • non-AD dementia • dementia with Lewy body • no evidence of dementia</td>
<td>11 mo(^a)</td>
<td>3 readers</td>
<td>89 (81 to 98)</td>
<td>92 (82 to 100)</td>
</tr>
<tr>
<td>Curtis et al (2015)(^{25}); Salloway et al (2017)(^{26})</td>
<td>16</td>
<td>End-of-life cohort</td>
<td>7.5 mo(^a)</td>
<td>Majorit y of 5 readers</td>
<td>86 to 92(^b)</td>
<td>86 to 100(^c)</td>
</tr>
<tr>
<td>Clark et al (2011, 2012)(^{21,22}) florbetapir</td>
<td>59</td>
<td>End-of-life cohort</td>
<td>≤24 mo</td>
<td>Majorit y of 5 readers</td>
<td>92 (78-98)</td>
<td>100 (80-100)</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td></td>
<td>7.5-24 mo</td>
<td>3-5 readers</td>
<td>86 to 93</td>
<td>86 to 100</td>
</tr>
</tbody>
</table>

Aβ: beta-amyloid; AD: Alzheimer disease; CI: confidence interval.

\(^a\) Mean.

\(^b\) Varied by criteria Aβ threshold.

An industry-funded multicenter study by Fleisher et al (2011) pooled data from 4, phase 1 and 2 trials of florbetapir PET imaging for a total of 210 participants, including 68 patients with probable AD, 60 patients with MCI, and 82 older unimpaired controls.\(^{24}\) There were significant differences in
mean standardized uptake value ratios across groups but considerable overlap in the range of values. The percentages of patients meeting threshold levels of amyloid with clinical AD, MCI, and cognitively healthy controls were 80.9%, 40.0%, and 20.7%, respectively. Among healthy controls, the percentage of patients with any florbetapir positivity on PET scan increased linearly by age, ranging from 11.8% for patients 55 to 60 years of age to 41.7% for patients 81 years of age or older.

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

**Section Summary: Clinically Valid**

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

**Clinically Useful**

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

**Direct Evidence**

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

In the trial by Pontecorvo et al (2017; discussed above), 342 patients with MCI and 276 patients with dementia were randomized to immediate or delayed reporting of Aβ PET results to their physicians (see Table 7). Changes in diagnosis and patient management are shown in Table 8. Prescription of acetylcholinesterase inhibitors decreased by 8%. The progression of cognitive change did not differ between positive Aβ and negative Aβ patients with suspected AD (p=0.763) during the year of follow-up. Due to the lack of power, it remains uncertain whether the changes in management improved health outcomes (see Tables 9 and 10).

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

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

None of these trials evaluated whether changes in management improved patient health outcomes. It cannot be determined from these studies whether the revised diagnoses were correct, and without longer follow-up the effect of the management changes on health outcomes is uncertain.

Chain of Evidence

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

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

Section Summary: Clinically Useful

Direct evidence on clinical utility (ie, improvement in net health outcomes resulting from testing) is lacking. Studies have reported a change in diagnosis and change in management but there is no evidence of an effect of Aβ PET on health outcomes. The single RCT identified had insufficient power to determine the effect of Aβ imaging on health outcomes (ie, quality of life, symptoms, function).

Summary of Evidence

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

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

SUPPLEMENTAL INFORMATION

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

The Appropriate Use Criteria (2013) for amyloid positron emission tomography were developed jointly by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association. They recommended that amyloid imaging as appropriate for individuals with all of the following characteristics:

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

Appropriate candidates include

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

Amyloid imaging is inappropriate in the following situations:

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

National Institute of Neurological and Communicative Disorders et al

1984 Diagnostic Criteria

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

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

Table 12. The 1984 Diagnostic Categories for Alzheimer Disease

<table>
<thead>
<tr>
<th>Diagnostic Categories for AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible</td>
</tr>
<tr>
<td>Clinical diagnosis of possible AD:</td>
</tr>
<tr>
<td>A. May be made on the basis of the dementia syndrome in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, the presentation, or the clinical course.</td>
</tr>
<tr>
<td>B. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia,</td>
</tr>
</tbody>
</table>
which is not considered to be the cause of dementia.
C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

Probable
Criteria for the clinical diagnosis of probable AD included:
A. Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests;
B. Deficits in 2 or more areas of cognition;
C. Progressive worsening of memory and other cognitive functions;
D. No disturbance of consciousness;
E. Onset between ages 40 and 90 years, most often after the age of 65 years; and
F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include:
A. Plateaus in the course of progression of the illness;
B. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sexual disorders, weight loss, and catastrophic verbal, emotional, or physical outbursts;
C. Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder; and
D. Seizures in advanced disease CT normal for age.

Features that make the diagnosis of probable AD uncertain or unlikely include:
A. Sudden apoplectic onset;
B. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
C. Seizures or gait disturbances at the onset or very early in the course of the illness.

Definite
Criteria for diagnosis of definite AD are:
A. Clinical criteria for probable Alzheimer disease; AND
B. Histopathologic evidence obtained from a biopsy or autopsy.

AD: Alzheimer Disease; CT: computed tomography.

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

In 2011, probable AD was defined by the National Institute on Aging and the Alzheimer's Association workgroup using the following diagnostic criteria:
"Meets criteria for dementia ... and in addition, has the following characteristics:
A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
B. Clear-cut history of worsening of cognition by report or observation; and
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
   a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text."
b. Nonamnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem-solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia should not be applied when there is evidence of:
   a. Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
   b. Core features of dementia with Lewy bodies other than dementia itself; or
   c. Prominent features of behavioral variant frontotemporal dementia; or
   d. Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or
   e. Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2013) issued a national coverage determination, through coverage with evidence development, that provides limited coverage for the use of Aβ PET imaging in 2 scenarios: (1) clinically difficult differential diagnoses, such as AD vs frontotemporal dementia, when the use of Aβ PET imaging may improve health outcomes, and the patient is enrolled in an approved clinical study, and (2) to enrich the Centers for Medicare & Medicaid Services-approved clinical trials of treatments or prevention strategies for AD. The Centers will cover one Aβ PET scan per patient in clinical studies that meet prespecified criteria.32

Ongoing and Unpublished Clinical Trials

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

Table 13. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned</th>
<th>Completion</th>
</tr>
</thead>
</table>

Original Policy Date: June 2012
**Ongoing**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Description</th>
<th>Enrollment</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02008357(^a)</td>
<td>Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 Study)</td>
<td>1150</td>
<td>Jul 2022</td>
</tr>
<tr>
<td>NCT02317250</td>
<td>Early and Long-Term Health Outcomes of Molecular Cerebral Imaging in Incipient Dementia (MCI-ID) II</td>
<td>1500</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>NCT03444870(^a)</td>
<td>Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of Gantenerumab in Patients With Early (Prodromal to Mild) Alzheimer's Disease</td>
<td>760</td>
<td>May 2023</td>
</tr>
</tbody>
</table>

**Unpublished**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Description</th>
<th>Enrollment</th>
<th>Date</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02781220</td>
<td>Implications for Management of PET Amyloid Classification Technology in the Imaging Dementia (IDEAS) Trial</td>
<td>69</td>
<td>Jul 2019</td>
<td></td>
</tr>
<tr>
<td>NCT01886820(^a)</td>
<td>A Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of [18F]NAV4694 PET for Detection of Cerebral Beta-Amyloid When Compared With Postmortem Histopathology</td>
<td>290</td>
<td>Sep 2018</td>
<td>Status unknown</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

\(^a\) Denotes industry-sponsored or cosponsored trial.

**ESSENTIAL HEALTH BENEFITS**

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits (“EHBs”), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state.

States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntary offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

**REFERENCES**


### CODES

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>78811</td>
<td>Positron emission tomography (PET) imaging; limited area (eg, chest, head/neck)</td>
</tr>
<tr>
<td></td>
<td>78814</td>
<td>Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; limited area (eg, chest, head/neck)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>A9586</td>
<td>Florbetapir F18, diagnostic, per study dose, up to 10 millicuries</td>
</tr>
<tr>
<td></td>
<td>Q9982</td>
<td>Flutemetamol F18, diagnostic, per study dose, up to 5 millicuries</td>
</tr>
<tr>
<td></td>
<td>Q9983</td>
<td>Florbetaben F18, diagnostic, per study dose, up to 8.1 millicuries</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>F01.50-F03.91</td>
<td>Dementia due to known physiological conditions, code range</td>
</tr>
<tr>
<td></td>
<td>G30.0-G30.9</td>
<td>Alzheimer disease, code range</td>
</tr>
<tr>
<td>ICD-10-PCS</td>
<td>C030YZZ</td>
<td>Nuclear medicine, central nervous system, positron emission tomography (PET) imaging, brain, other radionuclide</td>
</tr>
<tr>
<td></td>
<td>C030KZZ</td>
<td>Nuclear medicine, central nervous system, positron emission tomography (PET) imaging, brain, Fluorine 18</td>
</tr>
</tbody>
</table>

### POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/12/14</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 7, 2014; references 7-9, 14-17, 20-23, and 26 added; references 2-3, 6, and 24-25 updated; no change to policy statements.</td>
</tr>
<tr>
<td>06/11/15</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 19, 2015; references 4-5, 11, 17-18, and 28 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>07/13/16</td>
<td>Replace policy – coding update only</td>
<td>Added HCPCS codes C9458, C9459, Q9982 and Q9983.</td>
</tr>
<tr>
<td>09/08/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 24, 2016; references 20-22 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>09/19/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through July 9, 2018; references 5, 16-19, 29, and 31 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>09/19/19</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 09/19/2019. Policy updated with literature review through July 2, 2019; references added. Policy statement unchanged.</td>
</tr>
</tbody>
</table>