**Medical Policy**

**MP 6.01.55**

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

<table>
<thead>
<tr>
<th>BCBSA Ref. Policy: 6.01.55</th>
<th>Related Policies</th>
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<tbody>
<tr>
<td>Last Review: 09/19/2018</td>
<td>2.04.14 Biochemical Markers of Alzheimer Disease</td>
</tr>
<tr>
<td>Effective Date: 09/19/2018</td>
<td>6.01.54 Dopamine Transporter Imaging With Single-Photon Emission Computed Tomography</td>
</tr>
<tr>
<td>Section: Radiology</td>
<td></td>
</tr>
</tbody>
</table>

**DISCLAIMER**

Our 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 coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

**POLICY**

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

**POLICY GUIDELINES**

There are HCPCS codes specific to the current U.S. Food and Drug Administration–approved radiopharmaceuticals for this imaging:

A positron emission tomography scan would be reported using the CPT codes for positron emission tomography or positron emission tomography with computed tomography scanning (ie, 78811 or 78814).

**BENEFIT APPLICATION**

**BLUECARD/NATIONAL ACCOUNT ISSUES**

State or federal mandates (eg, 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.¹ A diagnosis of possible AD dementia is made when the patient meets the core clinical criteria for AD dementia but has an atypical course or an etiologically mixed presentation (see Table 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 neurofibrillar 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 Criteria&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Typical Course or Presentation&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Postmortem Confirmation&lt;sup&gt;c&lt;/sup&gt;</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>

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

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

<sup>c</sup> Presence of extracellular β-amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex.

Mild cognitive impairment (MCI) may be diagnosed when there is a change in cognition, but impairment is insufficient for the diagnosis of dementia.<sup>4</sup> 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%.<sup>5</sup>

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.<sup>6</sup>,<sup>7</sup>

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.<sup>8</sup>

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
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with cognitive impairment who are being evaluated for Alzheimer disease (AD) and other causes of cognitive decline.9-11

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 MEDLINE database. The most recent literature update was performed through July 9, 2018.

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 mild cognitive impairment (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 PICOTS were used to select literature to inform this review.

Original Policy Date: June 2012
**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).

**Comparators**
The criterion standard for the development of AD is postmortem neuropathologic examination. In the absence of comparisons with the criterion standard, clinical follow-up to determine conversion to probable AD may be used as a surrogate end point 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.

**Timing**
Diagnostic accuracy can only be confirmed at autopsy or after several years 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. There is currently no treatment for MCI. Direct evidence of an improvement in health outcomes would be observed in years when a disease-modifying treatment has been developed.

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

**Study Selection Criteria**
For the evaluation of 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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires 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 evaluating conversion from MCI to probable AD have been reported, some of which are described in Table 3 and 4. The largest prospective study is 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 ($p<0.001$, see Table 4), increasing to 8.45 when low hippocampal volume and poorer cognitive status was added to the model.

**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 (2014)</td>
<td>52 patients ≥50 y with recently diagnosed MCI</td>
<td>Longitudinal follow-up</td>
<td>4-point decline on the ADAS</td>
<td>Visual rating as Aβ+ (n=17) or Aβ- (n=30)</td>
<td>3 y</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Aβ+: positive Aβ PET scan; Aβ−: negative Aβ PET scan; ADAS: Alzheimer Disease Assessment Scale; MCI: mild cognitive impairment; NR: not reported; 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 Aβ+ to pAD</th>
<th>Conversion of Aβ− to pAD</th>
<th>HR (95% CI)</th>
<th>Clinical Validity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sens</td>
<td>Spec</td>
<td>PPV</td>
<td>NPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolk et al</td>
<td>232</td>
<td>224</td>
<td>54% of 97</td>
<td>23% of</td>
<td>2.51</td>
<td>64 69 54 77</td>
</tr>
</tbody>
</table>
### Table 5. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ong et al (2013, 2015)14,15</td>
<td></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>
</tr>
<tr>
<td>Doraiswamy et al (2014)13</td>
<td></td>
<td></td>
<td>3. Used a 4-point decline on ADAS rather than full clinical evaluation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

ADAS: Alzheimer Disease Assessment Scale; SUVR: standardized uptake value ratio.

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.

Outcome 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).

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

### Table 6. Study Design and Conduct Gaps

<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)(^{16})</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)(^{14,15})</td>
<td></td>
<td></td>
<td>1. Clinical evaluation at 4 y not blinded to PET scans</td>
<td></td>
<td></td>
<td>1. CIs not reported</td>
</tr>
<tr>
<td>Doraiswamy et al (2014)(^{13})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. CIs not reported</td>
</tr>
</tbody>
</table>

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

\(^{d}\) Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

\(^{e}\) Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

\(^{f}\) Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

### Section Summary: Clinically Valid

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

### Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.
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**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

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

| Table 7. Summary of Key Randomized Controlled Trial Characteristics |
|---------------------------------|----------------|----------------|----------------|----------------|
| Study                           | Countries      | Sites          | Dates          | Participants   |
| Pontecorvo et al (2017)         | U.S., EU       | 60             | 2012-2015      | 618 patients 50-90 y with MCI (n=342) or dementia (n=276) |
|                                 |                |                |                | 308 and physicians had immediate access to Aβ PET results |
|                                 |                |                |                | 310 and physicians had delayed (12 mo) access to Aβ PET results |

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

| Table 8. Summary of Key Randomized Controlled Trial Results |
|---------------------------------|----------------|----------------|----------------|----------------|
| Study                           | Change in Diagnosis | Change in Patient Management | Cognitive Performance | Function | Quality of Life |
| Pontecorvo et al (2017)         |                  |                           |                    |            |                |
| 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                               | <0.001           | <0.002                     | NR                | NR          | NR           |
| NNT                             | 3.8              | 8                          |                   |             |              |

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

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

| Table 9. Relevance Gaps |
|-------------------------|-----------------|-----------------|-----------------|-----------------|
| Study                   | Population      | Intervention    | Comparator      | Outcomes        |
| Pontecorvo et al (2017) | 1. Did not distinguish between patients with MCI or AD | 1. Health outcomes were |
The evidence gaps 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.

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. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.


Table 10. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pontecorvo et al (2017)</td>
<td>1, 2. Not blinded to treatment or outcome assessment</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>
</tr>
</tbody>
</table>

The evidence gaps 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.


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).

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 PICOTS 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).

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 end point 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.

Timing
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.

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

Study Selection Criteria
For the evaluation of 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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires 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>Readers</th>
<th>Sensitivity (95% CI or Range), %</th>
<th>Specificity (95% CI or Range), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabri et al (2015)22</td>
<td>74</td>
<td>AD, non-AD dementia, dementia with Lewy body, no evidence of dementia</td>
<td>11 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 readers</td>
<td>89 (81 to 98)</td>
<td>92 (82 to 100)</td>
</tr>
<tr>
<td>Curtis et al (2015)23; Salloway et al (2017)24</td>
<td>106</td>
<td>End-of-life cohort</td>
<td>7.5 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Majority of 5 readers</td>
<td>86 to 92&lt;sup&gt;b&lt;/sup&gt;</td>
<td>86 to 100&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clark et al (2011, 2012)&lt;sup&gt;19,20&lt;/sup&gt;</td>
<td>59</td>
<td>End-of-life cohort</td>
<td>≤24 mo</td>
<td>Majority 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>

AD: Alzheimer disease; CI: confidence interval.

<sup>a</sup> Mean.

<sup>b</sup> 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. 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.

At least 4 multicenter studies have reported on changes in diagnosis and patient management following Aβ PET imaging. These trials did not evaluate whether the changes in management improved patient health outcomes. For example, Boccardi et al (2016) reported on the results from the prospective, multicenter open-label Incremental Diagnostic Value of Amyloid PET with [18F]-Florbetapir study. The study included 228 consecutive adults with cognitive impairment who were evaluated by a dementia specialist for AD or other causes of cognitive decline. Patients underwent a routine diagnostic workup including ancillary tests. Before Aβ PET imaging, the specialists reported their confidence that the findings were consistent with an AD diagnosis. About 65% of patients with a prescan diagnosis of AD and about 50% of patients with a prescan diagnosis of non-AD had a positive scan. Following imaging, there was an increase in diagnostic confidence and change in medications, particularly for patients diagnosed with non-AD who had a negative scan. It cannot be determined from this study whether the revised diagnoses were correct, and without longer follow-up the effect of the management changes on health outcomes is uncertain.

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).

**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. 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 3 years. The negative predictive value of Aβ PET in these studies ranged from 77% to 95%. There are currently no disease-modifying drugs, and direct evidence of improved health outcomes with this technology is lacking. An RCT tested immediate vs delayed reporting of Aβ test results for patients with MCI and AD. No differences between the groups were found for health outcomes, although the study was not powered for these outcome measures. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

**SUPPLEMENTAL INFORMATION**

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

*Society of Nuclear Medicine and Molecular Imaging and Alzheimer’s Association*

The 2013 Appropriate Use Criteria 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
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>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis of possible AD:</td>
<td></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>
<td></td>
</tr>
<tr>
<td>B. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.</td>
<td></td>
</tr>
<tr>
<td>C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria for the clinical diagnosis of probable AD included:</td>
</tr>
<tr>
<td>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;</td>
</tr>
<tr>
<td>B. Deficits in 2 or more areas of cognition;</td>
</tr>
<tr>
<td>C. Progressive worsening of memory and other cognitive functions;</td>
</tr>
<tr>
<td>D. No disturbance of consciousness;</td>
</tr>
<tr>
<td>E. Onset between ages 40 and 90 years, most often after the age of 65 years; and</td>
</tr>
<tr>
<td>F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.</td>
</tr>
</tbody>
</table>

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;
β-Amyloid Imaging With Positron Emission Tomography for Alzheimer Disease

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 7 will cover 1 Aβ PET scan per patient in clinical studies that meet prespecified criteria.32

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently 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 Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01886820a</td>
<td>A Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of [18F]NAV4694 PET for Detection of Cerebral Beta-Amyloid When Compared With Postmortem Histopathology</td>
<td>290</td>
<td>Sep 2018</td>
</tr>
<tr>
<td>NCT02008357a</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>NCT03444870a</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>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02420756</td>
<td>Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study: A Coverage With Evidence Development Longitudinal Cohort Study</td>
<td>18,488</td>
<td>Dec 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
β-Amyloid Imaging With Positron Emission Tomography for Alzheimer Disease

Denotes industry-sponsored or cosponsored trial.

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>A9599</td>
<td>Radiopharmaceutical, diagnostic, for beta-amyloid positron emission tomography (PET) imaging, per study dose, not otherwise specified</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></td>
<td>Investigational for relevant diagnoses</td>
</tr>
<tr>
<td></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></td>
<td>ICD-10-PCS codes are only used for inpatient services</td>
</tr>
<tr>
<td></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>
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<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 20, 2017; references 2, 25, and 28-31 added. Policy statement unchanged.</td>
</tr>
</tbody>
</table>
literature review through July 9, 2018; references 5, 16-19, 29, and 31 added. Policy statement unchanged.