Beta-Amyloid Imaging With Positron Emission Tomography for Alzheimer Disease

Description

Three radioactive tracers (florbetapir fluorine 18, florbetaben fluorine 18, flutemetamol fluorine 18) that bind to β-amyloid (Aβ) and can be detected in vivo with positron emission tomography (PET) have been approved by the Food and Drug Administration. This technology is being evaluated to detect Aβ plaque density in adults with mild cognitive impairment (MCI) or dementia.

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 Alzheimer disease (AD).6,7

PET images biochemical and physiologic functions by measuring concentrations of positron-emitting chemicals in the body region of interest. Radiopharmaceuticals used for Aβ imaging may be generated in a cyclotron or nuclear generator and introduced into the body.
by intravenous injection. A number of carbon 11- and fluorine 18-labeled PET radiopharmaceuticals have been investigated for imaging brain Aβ.

**OBJECTIVE**

The objective of this evidence review is to evaluate whether β-amyloid imaging with positron emission tomography, as an adjunct to clinical diagnosis, improves the net health outcome in individuals with suspected Alzheimer disease.

**POLICY STATEMENT**

Beta-amyloid imaging with positron emission tomography is not medically necessary.

**POLICY GUIDELINES**

None

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA 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." 9, 10, 11

Table 1. 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 three 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."

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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**

**Summary of Evidence**

For individuals who have mild cognitive impairment (MCI) who receive β-amyloid (Aβ) imaging with positron emission tomography (PET), the evidence includes studies on diagnostic accuracy and a randomized controlled trial 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 Alzheimer disease (AD) as a reference standard, report that patients with a positive Aβ PET scan at baseline have an increased risk of conversion to probable AD at 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 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**

**Practice Guidelines and Position Statements**

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

The Appropriate Use Criteria (2013) for amyloid positron emission tomography were developed jointly by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association. 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.¹

Table 2 summaries the 1984 guidelines as related to the diagnostic categories.

**Table 2. The 1984 Diagnostic Categories for Alzheimer Disease**

<table>
<thead>
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<th>Diagnostic Categories for AD</th>
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<tr>
<td>Possible</td>
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Clinical diagnosis of possible AD:

A. May be made on the basis of the dementia syndrome in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, the presentation, or the clinical course.

B. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of dementia.

C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

| Probable |

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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:

1. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

2. Clear-cut history of worsening of cognition by report or observation; and

3. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

   1. 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.

   2. 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.

4. The diagnosis of probable AD dementia should not be applied when there is evidence of:

   1. 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

   2. Core features of dementia with Lewy bodies other than dementia itself; or

   3. Prominent features of behavioral variant frontotemporal dementia; or

   4. Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or

   5. 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.  

REFERENCES


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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tr>
<td>September 2013</td>
<td>New policy</td>
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<tr>
<td>September 2014</td>
<td>Replace policy</td>
<td>Policy updated with a literature review, adding references 7-9, 14-17, 20-23, and 26. No changes to the policy statement.</td>
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<tr>
<td>September 2015</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>
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<tr>
<td>September 2016</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>December 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 9, 2018; references 5, 16-19, 29, and 31 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>December 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 2, 2019; references added. Policy statement unchanged except investigational corrected to not medically necessary.</td>
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