Amyloid PET Imaging with Florbetapir for Diagnosis of Alzheimer's Disease

- [18F]-Florbetapir is a new FDA-approved agent that binds to amyloid deposits which can be imaged with PET
- [18F]-Florbetapir-PET may allow earlier diagnosis of Alzheimer’s disease (AD), aid in the diagnosis of non-AD neurodegenerative diseases, and provide prognostic information for patients with mild cognitive impairment (MCI)

Amyloid imaging may be beneficial:
- For patients with an objectively confirmed cognitive impairment
- When a diagnosis of AD is possible but not certain, particularly when atypical clinical features are present
- When knowledge regarding the presence of amyloid would increase diagnostic certainty and alter management

Amyloid imaging is not appropriate:
- For patients with core clinical criteria for AD and typical age of onset
- To determine the severity of dementia
- To screen asymptomatic patients

Over the past decade, the ability to image features of Alzheimer’s disease (AD) has grown considerably, which can have value in both clinical practice and research. The clinical diagnosis of AD carries some degree of uncertainty, and histopathological diagnosis is regarded as the reference standard before a diagnosis of AD is considered definitive. This difficulty in making a definitive diagnosis has driven a search for better tests. The current diagnostic criteria for AD rely on the identification of an appropriate syndrome of cognitive deficits, including insidious onset and progression of memory loss, impaired reasoning, and/or visuospatial disorientation as well as correlative biomarker findings such as a typical atrophy pattern on brain imaging or typical pattern of hypometabolism on fluorodeoxyglucose PET (FDG-PET) and CSF protein alterations. Additionally, the diagnosis of AD requires exclusion of other etiologies as the primary cause of dementia such as fronto-temporal lobar degeneration (FTLD), dementia with Lewy bodies (DLB), stroke, brain tumor, hydrocephalus, and depression although these conditions are often concurrent with AD.

At present, it is not necessarily helpful to have a definitive diagnosis of AD because no disease-modifying drug treatment is available. In many cases, however, a specific diagnosis may

Figure 1. Amyloid PET imaging performed with florbetapir in a 71-year-old man with objective clinical findings of impaired cognitive function principally involving decreased memory. The examination is negative for amyloid, consistent with sparse to no amyloid plaques in the brain. The results of this examination are not consistent with a diagnosis of AD although this result does not exclude the possibility of the development of AD in the future.
be very meaningful for symptomatic medical management, prognosis, and life planning, both for patients and for their families and caregivers. In particular, many patients with mild cognitive impairment (MCI) face a great deal of uncertainty in their futures, and determination of the underlying pathology may be particularly valuable for them because many do not progress to frank dementia even after a decade of follow-up, and as many as a third may recover and return to normal cognitive function.

Structural imaging for dementia patients, performed with CT or MRI, was first used to include or exclude causes of clinical cognitive impairment other than AD. Subsequently, structural imaging, particularly MRI, was found to be useful for more specific diagnoses because it can show characteristic although not pathologically specific alterations in patients with AD that begin with atrophy that is most pronounced in the hippocampus and temporal and parietal lobes, regions that correspond closely to the spread of neurofibrillary tangles seen in histopathological studies. In addition, MRI is occasionally useful because it can show signal abnormality indicative of comorbid vascular disease and microhemorrhage.

The PET radiotracer, FDG, has also been used for the evaluation of dementia. FDG is a glucose analog whose uptake corresponds to cortical metabolic activity. FDG-PET imaging of patients with AD typically demonstrates a pattern of temporal and parietal lobe hypometabolism that corresponds to regions of brain atrophy and which worsens over time in proportion to the progression of the underlying disease. FDG-PET is of particular value for distinguishing between DLB, FTLD, and AD, which can often be discerned by distinct patterns in the distribution of FDG uptake.

**Amyloid Imaging**

Amyloid deposition in the brain is a defining characteristic of AD, and amyloid plaques can be reliably imaged in the brain using radiolabeled tracers. The first widely used amyloid PET tracer was the research agent Pittsburgh Compound B (PiB), which launched the field of amyloid PET imaging. There is currently one FDA-approved, clinically available amyloid PET tracer: [18F]-florbetapir. Additionally, there are other amyloid PET tracers under development that are likely to achieve FDA approval in the near future, including flutametamol, florbetaben, and NAV4694. While very high quality research studies have demonstrated that florbetapir-PET reliably and accurately measures brain amyloid deposition, it should be regarded as a highly accurate biomarker for a molecular pathology and not an indicator of clinical dementia or a specific dementia syndrome such as AD dementia or mild cognitive impairment due to AD.

In studies of clinically diagnosed AD patients, 96% have been shown to have amyloid deposits through florbetapir-PET imaging; it has not yet been established whether the remaining patients were incorrectly diagnosed with AD or whether the test is not sensitive enough. There are also patients with other neurodegenerative, amyloid-associated diseases who are amyloid-positive but have a clinical diagnosis other than AD dementia, for instance the progressive non-fluent apahsia subtype of frontotemporal dementia, DLB, and cerebral amyloid angiopathy.
Identification of clinical syndrome (mild cognitive impairment, or MCI; dementia);
Clinical evidence of persistent or progressive cognitive decline;
Structured objective assessment of mental status such as the Mini-Mental State Examination, Montreal Cognitive Assessment, or a similar measure;
Known comorbidities;
List of prescribed medications and rationale for use of psychoactive medications, if any;
Results of neuropsychologic testing performed;
Results of structural brain imaging (such as MR imaging or CT) performed;
Relevant laboratory tests, which should include complete blood count, chemistry profile, B12, and thyroid hormone;
Reasons that the cause of cognitive impairment remains uncertain after completion of a standard clinical evaluation and treatment of comorbidities;
Treatment and care plan based on amyloid PET findings.

Amyloid Imaging Task Force of the Alzheimer’s Association and Society for Nuclear Medicine and Molecular Imaging

In studies of patients with MCI, around 60% have been shown to be amyloid-positive. In these studies, approximately one third of these MCI patients progressed to frank dementia within a period of three years; in this subset, 93% were amyloid-positive at baseline. However, a substantial number of amyloid-positive patients did not develop dementia within three years.

In summary of the current understanding of amyloid in the brain, amyloid PET imaging has utility with respect both to its positive predictive value and its negative predictive value. A large amount of amyloid in the brain is associated with a higher risk of AD dementia, although this diagnosis cannot be established by amyloid PET imaging alone. An absence of amyloid in the brain is not consistent with a diagnosis of AD, and other etiologies should be considered as a diagnosis for cognitive deficits. Additionally, a negative amyloid PET examination does not exclude the possibility of the development of AD in the future.

**Appropriate Use Criteria for Amyloid Imaging**

Given the current understanding of the significance of amyloid in the brain, guidelines for appropriate use of amyloid PET imaging have been created by a joint committee of the Alzheimer’s Association (AA) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI). These guidelines and a subsequent commentary have been published and are described below.

Before amyloid PET imaging is considered, a dementia expert should determine that the patient is cognitively impaired through objective testing of mental and neurophychological status. For appropriate use of amyloid PET, there should be an objective determination of persistent and unexplained cognitive deficits that could be caused by AD, although with significant uncertainty in diagnosis after a comprehensive evaluation by a dementia expert. Candidates for amyloid imaging also include those with progressive dementia starting at an atypically early age (usually defined as 65 years of age or less). Of note, amyloid imaging is only recommended for patients when it will increase certainty of diagnosis and alter clinical management.

Amyloid PET imaging is not appropriate for patients who meet core clinical criteria for AD with a typical age of onset for whom AD is the most likely diagnosis. Nor is it appropriate for patients with a cognitive complaint that has not been confirmed by objective testing. Amyloid PET imaging is not suitable for determining the severity of dementia and should not be used based solely on a family history of dementia or the presence of apolipoprotein e4 (a known risk factor for AD) or as a substitute for genetic testing. Amyloid PET imaging should not be used as a screening test on cognitively normal individuals.

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<thead>
<tr>
<th>Table 1. Recommended documentation for patients prior to amyloid imaging</th>
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<td>Age and date of onset of symptoms;</td>
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<td>Treatment and care plan based on amyloid PET findings.</td>
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To help ensure that amyloid imaging is used appropriately, the AA/SNMMI expert panel has developed a checklist (Table 1) describing relevant clinical information that should be documented for each patient, including cognitive status and evidence of decline together with test results (neuropsychological, prior brain imaging, and relevant laboratory tests). This checklist should be shared with the nuclear medicine specialist performing the examination and stored in the patient's medical record for extraction and review. It is expected that this should be sufficient to demonstrate the medical necessity of amyloid PET imaging to third-party payers.

**Scheduling**

Amyloid PET imaging can be performed on the Mass General main campus in Boston and at Mass General Imaging in Chelsea. Examinations can be ordered through the Radiology Order Entry (ROE) system or by contacting Wayne Marshall at 617-887-3505. Please note that a 10-day lead time is required to schedule this examination.

**Further Information**

For more information regarding amyloid PET imaging, please contact Mykol Larvie, MD, PhD, (617-726-8320) Nuclear Medicine and Neuroradiology, or Keith Johnson, MD, (617-724-7066) Nuclear Medicine, Massachusetts General Hospital.

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**References**


