Progress in Alzheimer’s disease research and imaging has made it possible to detect beta-amyloid in the human brain during life using radioactive tracers and positron emission tomography (PET). To provide guidance for physicians and their patients, the Alzheimer’s Association and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) convened the Amyloid Imaging Taskforce to develop criteria for the appropriate use of amyloid PET imaging compounds.\(^1\)\(^2\)

The following commonly asked amyloid imaging questions and answers are based on the appropriate use criteria — jointly published by the Amyloid Imaging Taskforce in *Alzheimer’s & Dementia*: The Journal of the Alzheimer’s Association and *The Journal of Nuclear Medicine*. This publication is available online at alz.org/AIT.

**What is the role of beta-amyloid in Alzheimer’s disease?**
The formation of plaques in the brain is one of the two neuropathological hallmarks of Alzheimer’s disease (AD); the other is tangles. Plaques are composed of a protein, beta-amyloid, that abnormally clumps together. Amyloid PET imaging detects the beta-amyloid built up not only in plaques, but also in the blood vessels supplying the brain. Because plaques are found in all patients with AD, it has been suggested that beta-amyloid plays an important role in the disease. Therefore, the amyloid hypothesis was formulated and is one of the many competing and complementary theories to help us understand the cause and/or progression of the AD. Recent data in individuals with familial AD (i.e., individuals with rare genetic mutations that develop AD) has shown that beta-amyloid can begin to accumulate 20-25 years before the clinical onset of the disease.\(^3\) This data along with other biochemical and genetic data suggests that beta-amyloid is involved in the pathophysiology of AD and may be one of the many important proteins to assess in understanding this disease. A positive amyloid PET scan in itself is not definitive for Alzheimer’s disease; this test is a diagnostic tool to determine whether or not there is beta-amyloid in the brain to help increase the clinical certainty of diagnosis. The appropriate use criteria help define who should be tested and who should order and/or read the test. (See below: *Does the presence of brain amyloid on a PET scan indicate Alzheimer’s disease?*)

**When should brain amyloid imaging be considered?**
For patients with all of the following core elements:
1. A cognitive complaint with objectively confirmed impairment.
2. Alzheimer’s disease is a possible diagnosis, but the diagnosis remains uncertain upon comprehensive evaluation by a dementia expert.
3. The presence or absence of amyloid would increase certainty in the diagnosis and alter the treatment plan.

**Which patients are appropriate for brain amyloid imaging?**
Appropriate patients for brain amyloid imaging are those who have met the above core elements and meet one of the following appropriate indications:
- Patients with persistent or progressive unexplained mild cognitive impairment.
- Patients who satisfy the core clinical criteria for AD due to any cause concomitant with an atypical course or of mixed etiology.
- Patients with progressive dementia and an atypical early age of onset (< 65 years of age).

**Which patients are inappropriate for brain amyloid imaging?**
It is inappropriate to use amyloid imaging:
- In patients who are age 65 or older who meet standard definitions and tests for AD, indicating a positive PET scan would provide little added value to the diagnosis.
- In asymptomatic patients or those with a cognitive complaint with no clinical confirmation of impairment.
- To try and determine dementia severity.
- In patients who request testing solely based on a family history of dementia or presence of other risk factors for AD, such as the ApoE-e4 gene.
- As a substitute for genetic testing for mutations that cause AD.
- For non-medical reasons, such as insurance, legal or employment decisions.

**Does the presence of brain amyloid on a PET scan indicate Alzheimer’s disease?**
Amyloid PET results do not establish a diagnosis of AD or other cognitive disorders. According to the FDA, it is “an adjunct to other diagnostic evaluations”— a tool giving physicians additional information to help clarify an otherwise unclear diagnosis. Amyloid PET imaging should only be used as part of a clinical workup in limited situations as determined by a dementia expert.
What is the significance of the absence or the buildup of beta-amyloid in the brain?

The presence of amyloid plaques in a patient with confirmed cognitive complaints increases the likelihood that the cognitive impairment is due to AD. The test is not a definitive diagnosis; it only determines the presence or absence of beta-amyloid. The potential clinical use of amyloid PET requires careful consideration so that its proper role is identified.

### Amyloid PET scan findings

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<tr>
<th>A negative scan with normal uptake in cortical grey matter (good grey-white matter contrast)</th>
<th>A positive scan with abnormally increased uptake in cortical grey matter (loss of grey-white matter contrast)</th>
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### Diagnostic implications

- A negative scan indicates few to no amyloid plaques. If there is cognitive impairment, the cause is likely to be something other than AD. This finding may alter treatment plans or need for further testing for AD.
- Other possible causes of cognitive impairment include strokes, thyroid disorders, B12 deficiency, drug interactions, depression and chronic alcoholism.
- A positive scan indicates moderate to frequent plaques. This may be found in patients with AD, in patients with other types of cognitive impairment, and in older people with normal cognition.

Images courtesy of Eli Lilly and Company and Avivid Radiopharmaceuticals.

**Who is considered a “dementia expert”?

The appropriate use criteria state that a dementia expert should be involved in determining whether or not an amyloid PET scan should be ordered because the proper application of the criteria depends heavily on the training, experience, and clinical judgment of dementia experts. The Amyloid Imaging Taskforce concluded that a dementia expert can be a self-identified physician as a physician trained and board-certified in neurology, psychiatry, or geriatric medicine, who devotes a substantial proportion of his or her medical practice, at least 25% (patient contact), to the evaluation and care of adult patients with acquired cognitive impairment or dementia, including probable or suspected AD, as confirmed by peer recognition.

**How much time does the amyloid imaging procedure take?

The test usually takes between 30 and 130 minutes, depending on the agent. Only 10-20 minutes are in a PET scanner.

**What compounds are used to obtain images of brain amyloid?

There are three agents for imaging beta-amyloid: florbetaben F 18 (Piramal Imaging/Neuraceq™), florbetapir F 18 (Lilly/Amyvid™), and flutemetamol F 18 (GE Healthcare/Vizamyl™).

**What are the adverse effects and precautions associated with amyloid-imaging agents?

Most commonly reported adverse reactions associated with the amyloid PET imaging agents are:

- **Florbetaben**: injection site pain (4%), injection site erythema (2%), injections site irritation (1%).
- **Florbetapir**: headache (2%) and less than 1% develop musculoskeletal pain, fatigue, blood pressure increase, and nausea.
- **Flutemetamol**: flushing (2%), increased blood pressure (1%), headache (1%), nausea (1%), and dizziness (1%).

Similar to other radiopharmaceuticals, these agents contribute to the patient’s overall long-term cumulative radiation exposure.

**Is amyloid imaging covered by Medicare?

Although the Alzheimer’s Association, SNMMI, and the Amyloid Imaging Taskforce supports Medicare coverage of amyloid imaging in limited populations as defined by the Amyloid Imaging Taskforce appropriate use criteria, Medicare does not cover it except for use in Coverage with Evidence Development (CED) programs, which are clinical trials that assess how amyloid imaging improves patient outcomes or advances patient treatment options. Commercial insurance coverage varies. Out-of-pocket costs for PET scans average $3,000 per test or greater.

**How were the appropriate use criteria for amyloid PET developed?

The Amyloid Imaging Task Force, composed of dementia and imaging experts, developed the criteria after assessing evidence supporting the use of imaging in different scenarios and rating the quality of the outcomes associated with the procedure. The criteria may change as more data becomes available about amyloid PET through further research and clinical experience.

**References**