

**Information about PET Amyloid Imaging for IDEAS Study Participants
October 31, 2015**

This document was prepared by the Alzheimer's Association in consultation with experts in research, clinical care, and ethics to help provide background regarding the use of beta-amyloid PET (positron emission tomography) imaging for Alzheimer's disease. The information discussed here covers current knowledge about appropriate and inappropriate use of such scans in a clinical setting, how scans are currently interpreted, and how scans are being used in research to measure the effectiveness of experimental therapies to treat or prevent mild cognitive impairment and dementia due to Alzheimer's disease. The IDEAS study team has added information relevant to patients who are being referred to the IDEAS study.

Definitions of dementia, mild cognitive impairment and Alzheimer's disease

In older adults, cognition (the ability to think, learn and remember) can be placed along a spectrum that on one end is described as healthy cognition and on the other end is described as dementia. Between them is a state called "mild cognitive impairment." Mild cognitive impairment (MCI) refers to a decline in memory or other cognitive functions that is beyond what is expected for age, yet does not interfere with independent day-to-day function. Dementia is defined as a decline in memory or other cognitive functions that is beyond what is expected for age, and interferes with independent day-to-day function. Over time, unfortunately most people with MCI develop dementia, although some people with MCI may also revert to normal cognition.

Alzheimer's disease (AD) is the most common form of dementia. It is characterized by the abnormal levels of two specific proteins in the brain: beta-amyloid plaques and neurofibrillary tangles. Plaques and tangles can be detected by looking at brain tissue under a microscope as part of a brain autopsy after death. A variety of tests can help in diagnosing Alzheimer's disease in living patients by looking at the effects of these microscopic abnormalities. Some examples of these tests are magnetic resonance imaging (MR), PET scanning to look at glucose activity using a tracer called FDG (FDG-PET), and cerebrospinal fluid analysis. These tests do not show how much beta-amyloid protein or neurofibrillary tangles are in the brain; however, certain new radioactive tracers that attach to beta amyloid can help to visualize more directly whether abnormal accumulation of beta-amyloid is present in the living brain by using a PET scan. The use of these tracers is referred to as beta-amyloid PET.

MCI and dementia can be caused by Alzheimer's disease (AD) pathology, or by other biological (pathological) changes in the brain. The presence of abnormal levels of plaques and tangles can be suspected based on clinical symptoms, such as prominent memory loss, even though abnormal levels of these proteins can only be definitively confirmed by microscopic examination. When this is the case, a doctor may diagnose someone as having MCI or dementia due to "probable Alzheimer's disease" (with the caveat that definite Alzheimer's disease requires microscopic confirmation, usually at autopsy). Now, with the introduction of new beta-amyloid PET imaging techniques, it is possible to detect the brain changes of AD during life.

What is the role of beta-amyloid in Alzheimer's disease?

The brain protein beta-amyloid is a key molecule in the diagnosis of Alzheimer's-related MCI and dementia. Beta-amyloid protein can clump together to form plaques in the brain, a hallmark of the disease, and remain in the brain for the remainder of a person's lifespan. Current evidence suggests that beta-amyloid build-up may be one of the earlier changes in the brain of someone with MCI or dementia due to Alzheimer's disease. This process may begin a decade or more before a person experiences the clinical symptoms associated with memory or functional impairment.

Amyloid plaques are a necessary part of an Alzheimer's disease diagnosis, but unless beta-amyloid accumulation is accompanied by signs of nerve cell death (tau protein tangles are markers of nerve cell death which is the other main microscopic feature of Alzheimer's disease), beta-amyloid accumulation may not result in MCI or dementia. Indeed beta-amyloid plaques are found in a significant proportion of older people with normal thinking and memory, and can also occur in individuals in whom other brain diseases cause the memory loss.

While there is compelling and consistent evidence that a person with elevated brain beta-amyloid has a substantial risk of eventually developing MCI or dementia, increased risk is not the same as certainty. There is intensive research going on now by Alzheimer's disease researchers to understand more about the risk profile of elevated brain beta amyloid. In the meantime, it is premature to use amyloid imaging to determine whether normal people could be at risk for Alzheimer's disease. In addition, clinical judgment is still needed to determine how relevant an elevation of brain beta-amyloid is in the diagnostic evaluation of someone with MCI or dementia that might also have other brain diseases.

What is beta-amyloid PET imaging?

Over the past decade, progress in Alzheimer's disease and molecular imaging research has made it possible to detect brain beta-amyloid using positron emission tomography (PET). The PET scan uses compounds (tracers) that are injected into a vein, travel through the bloodstream to the brain and adhere to beta-amyloid in the brain, allowing them to be seen by a PET scanner. Currently, beta-amyloid PET imaging is approved by the Food and Drug Administration (FDA), but is not reimbursed by Medicare. Medical guidelines are in place to help physicians determine how to appropriately use beta-amyloid PET in their practice (details below in the section entitled "Beta-amyloid Imaging Use in Clinical Practice.") There are three FDA-approved agents for imaging beta-amyloid: [¹⁸F] florbetapir (brand name Amyvid™), [¹⁸F] flutemetamol (brand name Vizamyl™), and [¹⁸F] florbetaben (brand name Neuraceq™).

What can beta-amyloid PET imaging show?

Beta-amyloid PET imaging can detect the density of beta-amyloid plaque in the brain. In general, an "amyloid positive" scan means that a moderate to frequent density of plaques is present (if you would count them under a microscope), while an "amyloid negative" scan denotes a sparse density or even fewer plaques. PET scan beta-amyloid imaging alone does not establish a diagnosis of Alzheimer's disease or other cognitive disorder, because clinical judgment is still

needed to determine how relevant an elevation of brain beta-amyloid is in the diagnostic evaluation of someone with MCI or dementia that might also have other brain diseases.

When the cause of MCI or dementia remains unexplained after a complete work-up, beta-amyloid PET brain imaging (in conjunction with a clinician's assessment, examination and cognitive testing) can help in reaching a diagnosis. Amyloid PET imaging may increase the physician's confidence that Alzheimer's disease is the underlying cause of the patient's MCI or dementia, or may diminish likelihood that Alzheimer's disease is the cause of an individual's symptoms.

Here is how an expert clinician might explain either amyloid-positive or amyloid-negative results from a beta-amyloid PET scan in an individual with cognitive impairment:

- If you do not have significant build-up of beta-amyloid in the brain (amyloid-negative scan), the cause of the symptoms is less likely to be Alzheimer's disease. Because you do not appear to have abnormal build-up of beta-amyloid, something other than Alzheimer's may be causing your memory loss or other cognitive complaints.
- If you do have significant build-up of beta-amyloid in your brain (amyloid-positive scan), Alzheimer's disease is more likely to be a contributing cause of your cognitive symptoms.

Current medical opinion suggests that, in a routine clinical setting, a person with normal cognition should not undergo beta-amyloid PET imaging because it is uncertain what the findings would mean. In research settings, however, some normal volunteers who do not have symptoms of MCI or dementia are undergoing beta-amyloid PET imaging as part of the trial design (e.g., prevention studies).

In what instances is beta-amyloid PET imaging being used?

Beta-amyloid PET imaging is being used to help understand the cause of cognitive decline. Clinical guidelines, called Appropriate Use Criteria (described below), have been developed to help identify for whom and in what setting beta-amyloid PET imaging may be appropriate. In research, beta-amyloid PET imaging is being used to help determine who is eligible for participation in clinical trials, to study changes in cognition to track the course of cognitive decline, and for evaluating potential therapies.

How is beta-amyloid PET imaging used in the IDEAS Study?

The Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study is a nationwide research study that will examine how beta-amyloid PET imaging helps physicians determine the cause of cognitive symptoms in patients with MCI or dementia, and evaluate whether the information provided by the scans can help improve patient outcomes. The study is being run by Alzheimer's disease and imaging researchers, the Alzheimer's Association, and the American College of Radiology. Amyloid PET scans in the IDEAS Study are conducted with FDA-approved imaging agents, and are paid for by the Centers for Medicare & Medicaid Services (CMS) as a covered service for Medicare beneficiaries who are participating in the trial (one scan per person). Medicare does not cover clinical beta-amyloid PET scans that are not being done as part of the IDEAS Study or other CMS-approved studies.

To be eligible for the IDEAS Study, patients must be Medicare beneficiaries 65 years of age or older, and must meet the Appropriate Use Criteria for amyloid PET imaging described below. Additional information about IDEAS will be discussed with you by your referring physician and is provided in the IDEAS Study consent form.

BETA AMYLOID IMAGING USE IN CLINICAL PRACTICE

The Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association formed the Amyloid Imaging Taskforce (taskforce) to develop guidelines for the appropriate use of beta-amyloid PET imaging in the clinical setting. The primary goal of the guidelines is to provide health care practitioners with information necessary to deliver optimal care. The beta-amyloid PET imaging Appropriate Use Criteria (AUC) is available [online](#).

When should beta-amyloid PET imaging be used in the clinical setting?

Appropriate uses for beta-amyloid PET imaging include instances where an individual:

- Complains of persistent or progressive unexplained memory problems or confusion, and for individuals who have a history and cognitive testing that support diagnoses of either dementia or mild cognitive impairment.
- Meets criteria for possible Alzheimer's disease, but is unusual in his or her clinical presentation.
- Has progressive dementia and relatively early age of onset (for example, before age 65).

According to the taskforce, a beta-amyloid PET scan is typically not appropriate for routine clinical assessments of cognitive decline.

When is beta-amyloid PET imaging not advised in the clinical setting?

According to the AUC, use of beta-amyloid PET imaging is not appropriate when the individual is:

- Age 65 or older and meets the standard definitions and tests for mild cognitive impairment or dementia due to Alzheimer's disease. (Note that neuropsychological and other testing have been shown to be reasonably accurate when used by skilled and experienced clinicians in diagnosing older individuals with late-onset Alzheimer's disease.)
- Asymptomatic or has a cognitive complaint without clear clinical confirmation of impairment (i.e. either mild cognitive impairment or dementia), except in the setting of research studies.

According to the AUC, beta-amyloid PET imaging also is not appropriate in the following settings:

- As a means of determining the severity of dementia.
- When requested solely based on a family history of dementia or presence of other risk factors for Alzheimer's, such as the APOE-e4 gene.
- As a substitute for genetic testing for mutations that cause Alzheimer's.
- For non-medical reasons, such as insurance, legal or employment decisions.

The taskforce acknowledged that the healthcare provider makes the ultimate judgment regarding the care of each patient. Although identifying potential benefits, the taskforce concluded that beta-amyloid PET results will not constitute, and are not equivalent to, a clinical diagnosis of Alzheimer's disease dementia. Imaging is only one tool among many (such as neuropsychological testing, other imaging tests, and cerebrospinal fluid tests) that clinicians may use judiciously in the complex diagnosis of dementia. Beta-amyloid PET imaging cannot substitute for a careful history and examination, including possibly other diagnostic tests like brain MRI, FDG-PET or cerebrospinal fluid analysis.

Only Medicare beneficiaries age 65 or older who meet the AUC for clinical beta-amyloid imaging are eligible to participate in the IDEAS Study. The IDEAS Study will not enroll patients in whom clinical amyloid PET is specifically not advised according to the AUC.

Who should order (request) or read (interpret) a beta-amyloid PET scan?

Beta-amyloid PET imaging should be performed according to standardized protocols by trained staff. The Appropriate Use Criteria for beta-amyloid imaging state that a dementia expert should be involved in determining whether it is appropriate to order a beta-amyloid PET scan. All physicians who refer patients to the IDEAS Study have stated that they meet these qualifications.

Beta-amyloid PET scans should be interpreted by a nuclear medicine physician or radiologist properly trained to interpret PET scans, and who have undergone tracer-specific interpretation training. All physicians interpreting beta-amyloid PET scans in the IDEAS Study have stated that they meet these qualifications.

How are clinical beta-amyloid PET scans read (interpreted)?

Clinicians may use terms like “positive” or “negative” when discussing a patient’s beta amyloid testing results. A nuclear medicine physician or radiologist reads (interprets) a scan as either amyloid-positive or amyloid-negative based on visual inspection using methodology developed and validated by the tracer manufacturers and approved by the FDA. While beta-amyloid buildup in patients occurs on a continuum, beta amyloid PET scans are read as either amyloid-negative or amyloid-positive. An “amyloid positive” scan means that a moderate to frequent density of plaques is present (if you would count them under a microscope), while an “amyloid negative” scan denotes a sparse density or even fewer plaques.

While some nuclear medicine physicians/radiologists use numerical measures (quantitation) to aid in analysis of beta-amyloid PET scans for clinical use or research, FDA-approved tracers used in the IDEAS study do not require quantitation in order for the scans to be interpreted. Beta-amyloid PET scans in the IDEAS Study will be interpreted as amyloid-positive or amyloid-negative based on the nuclear medicine physician/radiologist’s visual inspection of the scan.

If a person has cognitive impairment and an “amyloid-negative” PET image, does this mean that this person does not have Alzheimer's disease?

This is a very complex question and one that is under intense study by the scientific community. In various studies, as many as 15-25%, of individuals who are diagnosed with AD dementia based on their clinical symptoms (not brain PET imaging) do not have evidence of elevated beta-

amyloid when measured by beta-amyloid PET imaging¹. The rate of beta-amyloid negative individuals is higher among people who are clinically diagnosed with early or very mild Alzheimer's dementia (as high as 20-25% in some studies). Current scientific knowledge suggests that an individual with dementia and an amyloid-negative PET scan has a diminished chance that Alzheimer's disease is the primary underlying cause of their dementia. In this instance, further evaluation by healthcare professionals should be conducted to establish the primary cause of the patient's symptoms. There are other causes of cognitive impairment and dementia that should be evaluated such as vascular dementia, dementia with Lewy bodies, frontotemporal dementia, certain general medical conditions, side effects of medications, or others.

The overall effectiveness of beta-amyloid PET assumes that the clinician who is ordering the scan and providing a diagnosis has experience in the assessment of individuals with dementia. It is also important to recognize that, just as with any other diagnostic scan, scan results may not always be accurate due to technical problems, interpretation errors and other causes.

Occasionally the results of a beta-amyloid PET scan may be equivocal, meaning that the results were not clearly positive or negative. In this case, other diagnostic tests, a second reader's review of the scan or a repeat beta-amyloid PET scan in the future may be considered by the referring physician. However, Medicare will only cover one beta-amyloid PET scan as part of the IDEAS Study.

Should cognitively impaired people with an amyloid-negative scan result receive additional assessments, such as a second opinion, about their diagnosis?

If an individual has MCI or dementia but does not have significant build-up of beta-amyloid plaques as seen on amyloid PET, current evidence indicates the person is unlikely to have Alzheimer's disease. Further evaluation by healthcare professionals should be conducted to determine whether there are other causes of dementia that may have different prognosis and treatment options.

BETA AMYLOID IMAGING USE IN RESEARCH STUDIES OTHER THAN THE IDEAS STUDY

What is the role of beta-amyloid PET imaging in research studies or clinical trials?

There are a number of additional research studies, such as clinical trials, that are using beta-amyloid PET imaging as either an eligibility criterion to enroll participants or to monitor the impact of investigational treatments on the levels of beta-amyloid in the brain (further information is available on [Alzheimer's Association TrialMatch](#)). Some of these studies will reveal amyloid status to participants, but not all of the trials allow the patient to know whether their scan is amyloid-positive or amyloid-negative. In addition, the exact criteria for eligibility based on amyloid-positive PET scans may vary from study to study.

¹ Salloway S, Sperling R, Fox NC, Blennow K, Klunk, W, Raskind M, et al. Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease N Engl J Med 2014; 370:322-333

For asymptomatic individuals in particular, the Appropriate Use Criteria for beta-amyloid PET imaging state that individuals without symptoms of MCI or dementia are not appropriate candidates for beta-amyloid PET scans in the clinical setting at this time. These individuals are NOT eligible for the IDEAS Study. However, the research community is actively seeking asymptomatic individuals for other studies such as prevention trials. In these cases, research studies provide education about the risks and benefits of beta-amyloid PET imaging, assess the participant's readiness and willingness to receive the result, and, where positive beta-amyloid PET results are disclosed, monitor the individual's well-being.

OTHER ACCESS to BETA AMYLOID IMAGING

Is there a way for an individual to get a beta-amyloid PET scan independent of a research study or clinical evaluation based on symptoms of memory decline?

A dementia specialist can refer a patient for beta-amyloid PET scanning if he/she feels that the information provided would be appropriate for patient management. This expert clinical evaluation is critical for determining whether a beta-amyloid PET scan would be helpful to an individual, for interpreting the significance of a beta-amyloid PET scan result, and for ruling-out potentially reversible causes of cognitive impairment (regardless of whether the beta-amyloid PET is positive or negative). Therefore, individuals are strongly discouraged from seeking beta-amyloid imaging without first undergoing a thorough evaluation by a clinician with expertise in the assessment of cognitive complaints and dementia.

Note that beta-amyloid PET scanning is not reimbursed by Medicare and is not covered by private medical insurance in most cases.