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Testing and disclosures related to amyloid imaging and Alzheimer's disease: Common questions and fact sheet summary

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Abstract Alzheimer's disease research has often focused on the molecular brain changes that promote memory loss and other dementia-related cognitive impairments. Many studies, for example, have used positron emission tomography (PET) imaging to measure brain levels of the beta-amyloid protein, a key molecular suspect in Alzheimer's. In recent years, PET scans have become more prominent in clinical settings. Clinicians may use a positive PET scan—that is, a significant presence of beta-amyloid plaques in the brain—to help determine a diagnosis of Alzheimer's disease. Yet, because beta-amyloid PET remains a fairly new diagnostic tool, physicians and patients still have many basic questions about how and why it is used. This article addresses some of those questions. It explains what PET scans actually show, how they are employed in research and clinical trials, and when they should and should not be used to help diagnose Alzheimer's in everyday patients. The article also discusses whether cognitively healthy people should request PET scans to assess their risk for developing dementia. Information in the text will be updated in future years, as diagnostic imaging techniques for Alzheimer's disease continue to evolve.

Keywords: Alzheimer's disease; Positron emission tomography (PET); Beta-amyloid; Plaques; Alzheimer's Association; National Institute on Aging (NIA); National Institutes of Health (NIH); Dementia; Mild cognitive impairment (MCI); Tau tangles; Magnetic resonance imaging (MRI); Appropriate use criteria (AUC); Amyloid Imaging Taskforce (AIT); Cortex

1. Introduction

When seeking medical attention for concerns regarding memory or cognitive functioning, there are many questions an individual or family may have regarding the diagnostic process, use of emerging technologies, what test results mean to them, and similar topics. Over the past decade, progress in Alzheimer's disease (AD) and molecular imaging research has made it possible to detect brain beta-amyloid using positron emission tomography (PET), a type of imaging [1]. Brain beta-amyloid PET imaging can detect beta-amyloid plaques in the brain, a pathological hallmark of AD [2]. Generally, a positive scan supports the presence of a significant density/concentration/burden of beta-amyloid plaques in the brain, whereas a negative scan denotes a low density/concentration/burden or absence of plaques [3–7]. PET scan beta-amyloid imaging alone does not establish a diagnosis of AD or other cognitive disorder; this is discussed in section 4 below.

The emergence of beta-amyloid PET, while primarily still in a research context, is raising complex questions for both the individual and the family, as well as for their physicians

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and medical professionals, surrounding the diagnostic process for AD and associated disorders. There is a particular focus on beta-amyloid PET, including questions concerning what it is, what it shows, and what it means in terms of diagnosing AD. The Alzheimer's Association, in collaboration with representatives from the National Institute on Aging (NIA) at the National Institutes of Health (NIH) and experts in research, clinical care, and ethics, led the effort to clarify the current state of knowledge on the use of beta-amyloid PET imaging for AD and associated disorders. As new diagnostic technologies develop, questions arise about the definitions of terms, the use of technologies in diagnosis, and how results obtained may apply to individual patient(s). The information discussed here covers current thinking about appropriate and inappropriate use of beta-amyloid PET in a clinical setting, how scans are currently interpreted, and how scans are being examined for use in research to measure the effectiveness of experimental approaches to treatment or prevention of mild cognitive impairment and dementia due to AD. As a result of this effort, this manuscript seeks to address common questions asked by individuals, families, and medical professionals regarding beta-amyloid PET imaging and presents a summary of the current state of the science related to its use.

Scientists and clinicians continue to learn more about the course of AD and its associated brain changes. As a result, the language used to describe AD also changes. Of particular interest is that AD may be identified by its neuropathology (brain changes), clinical presentation (cognitive symptoms such as memory changes), or both. Updates to this document will continue to reflect the emerging state of understanding of this disease and its relationship to amyloid imaging and other imaging technologies as they evolve.

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

In older adults, cognition—the ability to think, learn and remember—can be mapped 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" (MCI), which 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 that interferes with independent day-to-day function. Over time, most people with MCI develop dementia, although some people with MCI remain stable or revert to normal cognition.

AD refers to abnormal changes in the brain that lead to cognitive decline; it can be defined pathologically by cellular and molecular changes. Specifically, AD is characterized by the presence of two types of protein aggregates (or clumps of "sticky proteins"): (1) amyloid plaques composed of beta-amyloid protein and (2) neurofibrillary tangles, composed of tau protein. Plaques and tangles are detected by examining brain tissue under a microscope as part of a brain autopsy after death. Various tests may be able to assist in diagnosing AD, including magnetic resonance imaging (MRI), PET using the glucose analogue [^{18}F] fludeoxyglucose (FDG), and cerebrospinal fluid analysis. However, certain new PET scan technologies use radioactive tracers to more directly visualize abnormal accumulation, if any, of beta-amyloid in the living brain. Emerging tools are also being developed to detect the abnormal accumulation of tau using PET imaging in the brains of living people. PET scans that detect amyloid plaques may be used in the clinic or in research studies (see below), while PET scans that detect tau tangles are currently only being performed as part of research studies.

MCI and dementia can be caused by AD pathology, or by other biological (pathological) changes in the brain. Although abnormal levels of plaques and tangles can only be definitively confirmed by microscopic examination, their presence can be suspected based on clinical symptoms, such as prominent memory loss. When this is the case, a doctor may diagnose someone as having MCI or dementia due to "probable AD" (with the caveat that definite AD requires microscopic confirmation, usually at autopsy). Doctors may order certain tests, including neuropsychological test batteries taken over a period of time, and they may seek to use other emerging tools such as blood tests, brain scans, or spinal fluid analysis in cases where standard approaches are not definitive in determining the cause of cognitive decline. Beta amyloid PET brain scans are a new technology that allows doctors to directly visualize whether amyloid plaques, one of the two key AD protein deposits, are accumulating in the living brain.

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

The brain protein beta-amyloid is a key molecule in the diagnosis of AD-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 life. Current evidence suggests that beta-amyloid build-up may be one of the earlier changes in the brain of someone with MCI due to AD or AD dementia. 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 AD diagnosis, but unless accompanied by tau tangles, the other main microscopic feature of AD, beta-amyloid accumulation may not produce MCI or dementia. Indeed, beta-amyloid plaques are found in a significant proportion of older people with normal thinking and memory, and they 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 progressing to MCI or dementia, increased risk is not the same as certainty [8,9]. Intensive current research is aimed at understanding more about the risk profile of elevated brain beta-amyloid in AD. In the meantime, it is premature to use amyloid imaging to determine whether healthy people who do not have cognitive impairment could be at risk for AD. Expert clinical judgment is still needed to determine the relevance of brain beta-amyloid elevation in the diagnostic evaluation of an individual with MCI or dementia who might also have other brain diseases.

4. What is beta-amyloid PET imaging?

Over the past decade, progress in AD and molecular imaging research has made it possible to detect brain beta-amyloid using PET. In the PET scanning method, the compound is injected into a vein, travels through the bloodstream and into the brain, adheres to the beta-amyloid in the brain, and "lights up." Currently, beta-amyloid PET imaging is a tool used primarily in clinical research studies and trials. For still-limited clinical use, guidelines exist to help determine the appropriate use of beta-amyloid PET imaging [10,11]. These criteria, known as the Appropriate Use Criteria (AUC), acknowledge that the health care provider makes the ultimate judgment regarding the care of each patient [10,11]. Although identifying potential benefits, the AUC concludes that beta-amyloid PET results will not constitute, and are not equivalent to, a clinical diagnosis of AD dementia. Imaging is only one tool among many, such as neuropsychological testing, other imaging tests, and cerebrospinal fluid analysis that clinicians may use judiciously in the complex diagnosis of dementia. As of December 2015, the U.S. Food and Drug Administration (FDA) has approved three agents for imaging beta-amyloid: [F-18] florbetapir (brand name, Amyvid), [F-18] flutemetamol (brand name, Vizamyl), and [F-18] florbetaben (brand name, Neuraceq). PET tracers that can detect tau are being developed and tested in research studies [12–14], but are not currently proven or FDA approved for use in the clinic.

4.1. What can beta-amyloid PET imaging show?

Brain beta-amyloid PET imaging can detect beta-amyloid plaques in the brain. In general, a "positive" scan supports the presence of moderate to frequent beta-amyloid plaques, whereas a negative scan denotes sparse or fewer plaques. PET scan beta-amyloid imaging alone does not establish a diagnosis of AD or other cognitive disorder. The FDA label clearly states this [15–17].

When the cause of MCI or dementia remains unexplained after a traditional clinical evaluation, brain beta-amyloid PET imaging in conjunction with this evaluation can help in reaching a diagnosis. Such imaging may increase the certainty that AD may be the underlying cause of the MCI or dementia. A negative beta-amyloid PET image could be used to diminish the chance that AD is the cause of an individual's symptoms.

An expert clinician might explain the results of a beta-amyloid PET scan in an individual with cognitive impairment as follows [10,11]:

- If you do not have significant build-up of beta-amyloid in the brain, the cause of the symptoms is less likely to be AD. Because you do not appear to have abnormal build-up of beta-amyloid, something other than AD may be causing your memory loss or other cognitive complaints.
- If you do have significant build-up of beta-amyloid in your brain, AD 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 of the lack of certainty for the person as to the meaning of any findings in this setting [10,11]. However, in a research setting, asymptomatic volunteers in some studies (e.g., prevention studies) are undergoing beta-amyloid PET imaging as part of the trial design.

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

In research, beta-amyloid PET imaging is being used to determine eligibility for clinical trial participation, and it may be useful for testing of potential therapies. For limited use in clinical practice, guidelines have been developed to help identify the individuals and settings in which beta-amyloid PET imaging may be appropriate.

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Alzheimer's Association formed the Amyloid Imaging Taskforce (AIT) to develop guidelines for the appropriate use of beta-amyloid PET imaging in the clinical setting [10,11].[A1] The primary goal was to provide health care practitioners with information necessary to deliver optimal care. The brain beta-amyloid PET imaging appropriate use criteria (AUC) were made available by *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* on January 28, 2013 [10] and by SNMMI's *Journal of Nuclear Medicine* [11].

According to the AUC, amyloid imaging is appropriate in individuals with MCI or dementia in whom the cause of cognitive impairment is uncertain after a standard evaluation by a clinician experienced in the diagnosis of cognitive disorders. A standard diagnostic evaluation includes a detailed history, physical and neurological examinations, tests of memory and other cognitive functions, blood tests to exclude general medical conditions that can impact cognition, and brain imaging in the form of CT or MRI. In addition, the referring clinician must determine that knowledge of amyloid status is expected to change the patient's diagnosis

and management. Examples of patients who would meet these criteria may include an individual who has persistent or progressive MCI of unknown cause; or an individual who has dementia and in whom AD is suspected but not certain due to atypical symptoms, unusually young age, or the presence of other significant medical, neurological, or psychiatric conditions that may be contributing to cognitive decline.

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

According to the AUC, a beta-amyloid PET scan would not typically be appropriate for everyday clinical assessments of cognitive decline [10,11]. However, in some circumstances, beta-amyloid PET imaging can be considered when an individual:

- Complains of persistent or progressive unexplained and/or atypical memory problems or confusion with a history and cognitive testing that support diagnoses of either dementia or mild cognitive impairment.
- Meets the criteria for possible Alzheimer's, but has an unusual clinical presentation.
- Has progressive dementia and is relatively young at disease onset (for example, before age 65 years).

5.1.1. 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 [10,11]:

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

According to the AUC, beta-amyloid PET imaging also is not appropriate in the clinic [10,11]:

- 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 AD, such as the APOE-e4 gene.
- As a substitute for genetic testing for mutations that cause AD.
- For nonmedical reasons, such as insurance and legal or employment decisions.

Ultimately, the health care provider makes judgments regarding the care of each patient based on their individual circumstances. Beta-amyloid PET imaging cannot substitute for a careful history and examination, including possibly other diagnostic tests like brain MRI, brain FDG-PET, or cerebrospinal fluid analysis.

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

Beta-amyloid PET imaging should be performed by trained staff using standardized protocols. The AUC 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.

As stipulated by the FDA, the scan should be read by a nuclear medicine or other molecular imaging professional properly trained to interpret results. Individuals considering a beta-amyloid PET scan are encouraged to ask their physician about their level of experience with beta-amyloid PET imaging and whether the scan will be read by an experienced person who has successfully completed specialized training programs (as stipulated by the FDA's approved use of these agents).

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

Clinicians may use terms like "positive" or "negative" when discussing an individual's beta-amyloid testing results. A molecular imaging specialist (typically a nuclear medicine physician or radiologist) reads (interprets) a scan as either positive or negative based on defined imaging criteria set by the research protocol[A2] that tested and validated the scans; all of these criteria must conform to specific guidelines provided by the manufacturer. Depending on the specific agent used, images may appear in black and white or in color, but it is not clear that reading accuracy depends on the method of display. Although the level of beta-amyloid binding will occur on a continuum, in general a clinical beta-amyloid PET scan would be read as "negative" if no binding is evident in the cortex (cognitive regions) of the brain, and as "positive" if binding is evident in the cortex. Numerical measures to quantify the degree of binding are being evaluated on a research basis, but the FDA labeling does not provide for any numerical measures to categorize a scan as "positive" or "negative."

5.2.2. If a person has cognitive impairment and a "negative" or "not elevated" beta-amyloid PET image, does it mean that the 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 percent to 25 percent of individuals who are diagnosed with AD dementia based on clinical symptoms (not brain PET imaging) do not have evidence of elevated beta-amyloid levels on PET imaging [8,9,18]. The rate of negative beta-amyloid findings is higher among people who are clinically diagnosed with early or very mild AD dementia (as high as 20 percent to 25 percent in some studies).

Current scientific knowledge suggests that an individual with dementia and a negative beta-amyloid PET image has a diminished chance that AD is the primary underlying cause of dementia. Health care professionals should further evaluate such individuals to establish the primary cause of the symptoms. Other causes of cognitive impairment and dementia (e.g., vascular cognitive impairment, dementia with Lewy bodies, frontotemporal lobar degeneration, certain general medical conditions, side effects of medications, cognitive aging) also should be evaluated.

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

Occasionally, the results of a scan may be equivocal, meaning that the results were not clearly positive or negative. In this case, other 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.

5.3. Should cognitively impaired people with a negative beta-amyloid image receive additional assessments, such as a second opinion, about their diagnosis?

Current evidence indicates that an individual who has MCI or dementia but no significant build-up of beta-amyloid on PET is unlikely to have AD. Health care professionals should further evaluate such individuals to determine whether there are reversible causes of dementia or other neurodegenerative diseases that may have different prognoses and treatment options.

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

Research continues to examine how beta-amyloid PET imaging can be validated as a diagnostic tool for AD. Scientists are trying to pinpoint if and how measures of beta-amyloid in the brain or the absence of beta-amyloid can predict the development of AD in everyday clinical settings. Several clinical trials are using the results of 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 (see information on Alzheimer's Association TrialMatch® [19]). Some of these studies will reveal amyloid status to participants, but not all of the trials reveal this information. In addition, the exact criteria for eligibility based on "positive" beta-amyloid PET scans may vary from study to study.

According to the AUC for beta-amyloid PET imaging, individuals without symptoms of MCI or dementia are not appropriate candidates for beta-amyloid PET scans in the clinical setting at this time. However, the research community is actively seeking asymptomatic individuals for studies, such as prevention trials. In all individuals undergoing amyloid PET, but in particular in research studies involving cognitively normal people, it is important to provide education about the risks and benefits of beta-amyloid PET imaging, assess the participant's readiness and willingness to receive the result, and in cases with positive results, monitor the individual's well-being. An individual taking part in a research study involving amyloid PET should ask whether the study is taking steps to minimize disclosure of the result in the medical record [20].

6.1. What should individuals consider when seeking beta-amyloid PET scans independent of a research study or clinical evaluation based on symptoms of memory decline?

As noted above, it is premature to use beta-amyloid PET to determine whether healthy people could be at risk for AD [10,11]. Expert clinical judgment is needed to determine the relevance of elevated brain beta-amyloid in the diagnostic evaluation of an individual with MCI or dementia who might also have other brain diseases. Some individuals concerned about AD risk for themselves or a loved one have been reported to seek their beta-amyloid status by means of beta-amyloid PET scans. 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. An expert clinical evaluation is critical for determining whether a beta-amyloid PET scan would be helpful, for interpreting the significance of beta-amyloid PET scan results, and for ruling out potentially reversible causes of cognitive impairment (regardless of whether the beta-amyloid PET scan is positive or negative).

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Appendices: End Notes

[A1]The AIT guidelines refer to the appropriate use of PET amyloid imaging in clinical practice. It is important to note that amyloid PET is also being used in research studies investigating other populations, including individuals with normal cognition who may be at-risk for developing symptoms due to AD.

[A2]Clinical trials may use the terms "elevated" or "non-elevated" to recognize that there is a range of amyloid plaque accumulation detectable in asymptomatic individuals. Quantitative methods may be used to determine eligibility for specific studies based on level of amyloid build-up.