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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.