Published in final edited form as:
Neurodegener Dis Manag. 2013 February ; 3(1): 43–51. doi:10.2217/nmt.12.75.

Should we disclose amyloid imaging results to cognitively normal individuals?

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Abstract

Demonstration of brain accumulation of fibrillar amyloid beta protein via positron emission tomography (PET) with amyloid specific ligands may support the diagnosis of Alzheimer's disease (AD). There is increasing recognition of the potential use of amyloid imaging to detect *in vivo* the pathology of AD in individuals with no ostensible cognitive impairment. Research use of amyloid PET in cognitively normal patients will be key to pursuit of therapies able to delay cognitive impairment and dementia due to AD. We review the pros and cons of disclosing amyloid imaging results to cognitively normal individuals in clinical and research settings and provide draft recommendations.

Keywords

ethics; disclosure; amyloid PET; Alzheimer's disease

Introduction

Alzheimer's disease (AD) is an insidious neurodegenerative process that begins years before clinical manifestation. Biological markers of disease (biomarkers) can be used to support clinical diagnosis [1]. Demonstration of brain accumulation of fibrillar amyloid beta (Aβ) protein via positron emission tomography (PET) with an amyloid-specific ligand is one biomarker that may support AD diagnosis. The amyloid PET ligand Amyvid® was recently approved by the FDA for identifying the presence of Aβ in persons with cognitive impairment [2]. While amyloid imaging has promise as a clinical diagnostic tool for those with cognitive problems, there is also increasing recognition of its potential use in detecting the molecular pathology of AD in people who are cognitively normal.

In 2011, research criteria were introduced to define cognitively normal individuals with evidence of cerebral amyloidosis as having “preclinical AD [3].” These research criteria were proposed to stimulate studies assessing interventions that may delay or prevent the onset of AD-related cognitive impairment. The widespread availability of amyloid PET

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imaging agents may lead to a wave of these secondary prevention trials. In these trials, screening with amyloid imaging will exclude up to 80% of potential participants who do not have evidence of cerebral amyloid. Thus, thousands of patients will need to be screened to achieve adequate numbers of individuals with preclinical AD to demonstrate an intervention's effectiveness. In many cases, such as in large, long-term interventional studies, cost alone will dictate that only amyloid positive patients are enrolled [4]. As a result, participants enrolled into these trials will, *de facto*, receive their biomarker results based on their eligibility for the study (i.e., amyloid negative participants will not be enrolled).

In this article, we review data on the clinical significance of the presence of cerebral amyloid in cognitively normal individuals and discuss the pros and cons of sharing the results of amyloid PET imaging in the clinical and research settings. We provide preliminary recommendations for responsibly disclosing this information in the research setting, though we offer caution related to the use of this tool in the clinical setting at this time.

What information is provided by amyloid PET?

FDA approval of Amyvid (florbetapir, AV-45) marked the culmination of a decade of research development [5]. Amyloid PET ligands bind to the fibrillar Aβ of neuritic plaques that are the pathological hallmark of AD [6, 7]. The sensitivity and specificity of amyloid PET as a marker of clinical diagnosis is an ongoing focus of study. Among patients meeting National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD, 80-98% will have “positive” scans (typically defined by regional analyses of ligand binding, relative to the cerebellum) [8-10]. Patients with comorbid neurodegenerative processes or dementia with Lewy Bodies also may scan positive on amyloid PET [11].

Among older healthy control populations, 20-40% will scan positive for the presence of cerebral amyloid [10, 12]. The concept of preclinical AD postulates that individuals with asymptomatic cerebral amyloidosis are in the presymptomatic stages of the disease and will eventually develop dementia if they live long enough. But autopsy studies observe that about one-third of older adults die with cerebral amyloid without expressing a dementia syndrome [13] and the clinical implications of asymptomatic cerebral amyloid remain imprecisely defined.

Early studies suggest asymptomatic cerebral amyloid is not benign. Neuroimaging studies find that cerebral amyloid is associated with structural and functional brain changes in areas implicated early in AD. Analyses from the Alzheimer's Disease Neuroimaging Initiative (ADNI) suggest that increased amyloid PET retention is associated with greater whole brain atrophy and regional atrophy in the medial temporal lobe and precuneus [14, 15]. Studies in other cohorts have observed elevated amyloid PET retention is associated cross-sectionally with lower brain volume [16, 17] and with longitudinal rates of global brain atrophy [18, 19]. Increased cerebral amyloid in nondemented older adults is associated with atrophy in specific regions involved early in the AD process [20], most commonly the hippocampus

[21, 22] and the posterior cingulate / precuneus [23-25]. Asymptomatic amyloid positive individuals also demonstrate evidence of disrupted functional connectivity [26-28].

Elevated cerebral amyloid, as evidenced by low levels of CSF Aβ or elevated amyloid PET retention, is associated with modest cognitive deficits. For instance, elevated cerebral amyloid is associated with altered processing speed [29, 30], executive function [29], and episodic memory [29-31]. Elevated cerebral amyloid is also associated with longitudinal decline in cognitive [16, 30, 32] and functional abilities [33] in participants enrolled as healthy controls. Initial longitudinal studies have found that amyloid positive cognitively normal individuals are at significantly increased risk for AD dementia [34] while amyloid positivity in those with Mild Cognitive Impairment (MCI) is an established risk factor for progression to AD [14, 35-38]. Although these results suggest the presence of cerebral amyloid is not benign, the magnitude and timing of the risk remains unknown and there is currently no means to identify amyloid positive individuals who are most likely to decline.

Further limitations include insufficient understanding of the sensitivity and specificity of the technique. Ten to twenty percent of diagnosed AD cases may be amyloid negative. Moreover, recent analyses from ADNI suggest that the presence of abnormal brain amyloid levels alone is not sufficient to predict future cognitive decline. Only persons who demonstrated both cerebral amyloidosis and abnormal levels of phosphorylated tau were at increased risk for brain atrophy [39] and cognitive decline over a 3-year period [40]. Therefore, unidentified factors may protect some amyloid positive individuals or amyloid may be ancillary to the primary cause of cognitive decline.

Thus, a growing literature suggests that fibrillar amyloid accumulation in cognitively normal individuals is associated with future risk of cognitive decline, brain atrophy, and altered brain function. As yet, however, the presence of amyloid positivity does not equate to a diagnosis of AD.

We next consider the ethics of disclosing amyloid imaging status to cognitively healthy individuals. Researchers and clinicians alike are bound by the principle of *primum non nocere* or nonmaleficence—*do no harm*—which may support the need for more conclusive evidence before systematic sharing of amyloid PET results. Alternatively, respect for the autonomy of the individual may warrant a more individualized approach to this decision. Ultimately, truthfulness and honesty in the form of informed consent must be used to communicate what is known about procedures and results and the reasons that disclosure (or nondisclosure) will be practiced. In this spirit, it is important to consider the pros and cons of disclosure of amyloid status in persons who have no demonstrable cognitive impairment.

Arguments against disclosure

The clinical significance of amyloid PET remains undefined

There are only preliminary estimates of associated hazard ratios for clinical progression to dementia among amyloid positive persons and no current means exist to identify and distinguish those who may have protective factors from those who are more vulnerable to cognitive decline. There is inter-observer variation in the interpretation of scan results and it

is inevitable that some tests will be ambiguous or challenging to interpret [41]. Even in the setting of robust signal (positive or negative), precise information on the magnitude and timing of risk associated with asymptomatic cerebral amyloid is lacking. Thus, only incomplete information of limited clinical value exists to offer individuals wishing to learn their amyloid PET status.

The potential psychological risk of disclosure has not been adequately studied

We do not yet know how participants will react to amyloid disclosure. It has recently been asserted that the fear of becoming demented is widespread [42]. Fearful individuals who wish to learn their amyloid PET status may be at risk for increased anxiety or depression upon disclosure. In individuals with cognitive impairment, risk for suicide is highest for patients with preserved insight [43] and this risk may apply to cognitively normal amyloid positive individuals. To our knowledge, there are currently no studies in the United States of how cognitively normal persons interpret positive or negative amyloid PET results, nor any studies investigating the potential psychological impact of disclosure. The extent to which the fear of dementia impedes rational decision-making is testable.

Effective interventions are not available

While some lifestyle interventions and investigational treatments may reduce amyloid burden (see below), there is insufficient evidence (i.e. prospective randomized controlled trials) to support any intervention as a prevention for AD or dementia at this time [44].

Disclosure may have unwanted personal healthcare implications

In the clinical setting, amyloid positivity could have serious unwanted healthcare and insurance implications. Despite that clinical and research findings should remain confidential by law, these implications must be considered [45]. Unwanted disclosure of amyloid PET could impact the cost or willingness of payers to insure amyloid positive persons, especially long-term care insurers.

Disclosure may have unwanted social or legal implications

AD remains associated with unfortunate stigmata [46]. Public perception equates a diagnosis of AD with the loss of self and a complete inability to make decisions, despite that these consequences of the progressive disease tend to occur in the middle to late stages. Public perception of amyloid positivity, relative to perception of AD dementia, has not been studied. Being labeled as amyloid positive or having a diagnosis of preclinical AD may carry the same public perception and negative consequences as AD diagnosis. This may be especially problematic for individuals in the workplace.

Therapeutic misconception may occur

A wide assumption is that therapeutic benefit of an intervention is greatest when it is administered in the early stage of disease. This is especially true in the case of AD, in which irreversible neurodegeneration worsens over time. Patients may understand that a critical window for enhanced outcomes may exist and volunteer for research out of a sense of heightened personal urgency to gain access to otherwise unavailable interventions. Any

research protocol that employs an intervention in combination with amyloid imaging could be misconstrued as providing more efficacious treatment.

Disclosure of negative results may give false reassurance. A common practice in studies employing amyloid imaging is to define scan outcomes as *amyloid positive* or *amyloid negative*. The dichotomy may be based on global or region-specific measures of tracer uptake. In addition to challenges related to ambiguous scans, the occurrence of false negative scans (absence of signal despite the presence of neuropathology [47]) and negative scan results in diseased individuals whose amyloid levels are not yet demonstrable may lead to false reassurance.

Arguments in favor of disclosure

Respect for autonomy is a foundation of medical ethics

Healthy individuals make personal decisions based on their evaluation of the personal risks and benefits [48]. Given that the current discussion is limited to individuals that are cognitively intact and competent to make their own choices, investigators and clinicians alike cannot (1) presume that the presence of cerebral amyloid affects the individual's judgment, nor (2) presume which aspects of the risks and benefits are most salient to the individual.

The use of amyloid PET may pave the road to AD prevention

Amyloid PET is more appealing to potential research participants than is lumbar puncture (Grill, *unpublished findings*) and thus may enhance the ability to conduct secondary prevention trials in those at greatest risk for AD. Such studies will have substantial impact on current and future healthcare. Beside clinical trials that restrict enrollment to amyloid positive persons, studies will not obligate participants to learn their amyloid PET results. Thus, to the extent that some volunteers may choose to participate only if they are provided results, doing so may expedite research conduct. In the clinical setting, early intervention may someday be key to successful treatment in AD.

Previous research suggests risk information can be delivered without psychological harm

Given the uncertainties of the clinical significance of asymptomatic cerebral amyloid, a positive amyloid scan does not equate to a diagnosis of AD; rather, the interpretation of a positive scan is limited to one of AD risk. Strong parallels can thus be made with previous studies of risk disclosure. The Risk Evaluation and Education for AD (REVEAL) study randomized cognitively normal first generation offspring of parents with AD to disclosure or non-disclosure of apolipoprotein E (APOE) genotype [49]. Disclosure did not increase depression, anxiety, or distress. Despite this, APOE disclosure to cognitively normal persons remains an uncommon clinical and research practice.

Disclosure may facilitate participant lifestyle changes

Finally, in the REVEAL study, participants who learned they were ε4 carriers were more likely to purchase long-term care insurance [50] and to report lifestyle changes such as taking vitamins and supplements [51]. Once amyloidosis is initiated, it is unlikely that brain

amyloid burden will return to normal levels without intervention [52]. Several lines of research, however, suggest that the amyloid risk for AD may be modifiable. Head trauma accelerates amyloidosis [53]. Retrospective and cross sectional studies suggest that exercise [54] and blood pressure [55] may moderate brain Aβ levels. Prospective studies have shown that diet [56] and immunotherapies [57, 58] can alter Aβ accumulation over time. Informing participants of their amyloid PET status may motivate them to take steps toward reducing AD risk and planning for the future.

Recommendations and conclusions

Recommendations for the clinical setting

We conclude that it is premature to routinely offer cognitively normal patients amyloid PET results routinely in a clinical setting. Regulations for the clinical use of amyloid PET in cognitively normal persons do not currently exist. There are insufficient data, understanding, and intervention options to support widespread clinical use and disclosure of amyloid PET in cognitively normal persons.

Most guidelines conclude that only when results have direct implications on treatment decisions should they be shared [59]. Thus, it is probable that only the availability of approved treatments capable of delaying onset of cognitive impairment would change this recommendation. Indeed, the FDA-approved label for Amyvid® specifies its use only in persons with cognitive impairment [2]. The clinical reality at this point is that lifestyle and other medical recommendations should be no different for cognitively normal individuals concerned about AD who are amyloid positive than for those who are amyloid negative, obviating the need to perform the scan.

As with off-label use of FDA-approved medications, clinicians may choose to break from FDA guidelines on a case-by-case basis. If doing so, they might consider the recommendations that we make below for safe and ethical disclosure.

We believe that further research is necessary to define more precisely the clinical significance of being amyloid positive, in particular the magnitude and timing of risk associated with the presence of asymptomatic amyloid. Additionally, we believe that more research is necessary before consensus can be reached regarding how those results should be communicated to patients. To achieve improved understanding of amyloid PET implications, risk knowledge, and indeed improved interventions, continued research use of amyloid imaging in cognitively normal volunteers is imperative [60].

Recommendations for the research setting

We conclude that cognitively normal research participants can be given the opportunity to learn their amyloid status after informed consent when accompanied by pre- and post-testing counseling. Some risks associated with disclosure are reduced in this setting. For example, research confidentiality may reduce the potential legal and healthcare implications. Moreover, research use of amyloid PET may result in tremendous societal benefit. As a result, we feel that the risk/benefit ratio is shifted toward disclosure in the research setting.

Research participants frequently feel they have the “right” to individualized results [61, 62] and though they may differ in their preferred methods of learning results, many do want access to personal information [63]. The fact that a study includes amyloid PET may cause some participants who had not otherwise considered undergoing testing to desire to learn their results [64]. Researchers must respect the autonomy and the desires of the participants who make these studies possible. Still, disclosure should occur only after extensive education, counseling, and assurance of truly informed consent.

Informed consent regarding the choice whether to learn amyloid PET status must be ensured. The consent process must be designed to facilitate informed decisions [65, 66]. Participants should be provided the current evidence regarding the clinical significance of both a positive and negative scan. This discussion should be framed as relevant to their future risk of developing AD and not as a diagnostic test for AD. Studies are needed to identify factors that may positively or negatively bias an individual's decision to participate. The consent process must rigorously oversee such factors and establish practices that ensure decisions are made without any undue influence. It may indeed turn out that, when fully informed through pre-test counseling, a large portion of cognitively normal individuals will change their minds and decline learning amyloid status [42].

How cerebral amyloid status is disclosed will be a critical factor in patient responses. A lack of respect for a potentially negative reaction promotes its eventual occurrence. Monitoring patient reactions is an important consideration. Clinical instruments to measure mental health outcomes are available. Studies disclosing amyloid status should collect measurements of anxiety, depression, and any coercion throughout the life of the research protocol. Deleterious effects must be limited and psychological symptoms treated, if or when they arise. Two obvious possibilities include negative reactions to positive scan results (psychological impact, potential for suicide) and negative reactions to negative scan results (the potential for a false sense of security). For the former especially, careful monitoring is essential and observed cases may warrant study amendment or closure.

The extent of current (limited) knowledge must be shared. Incumbent upon researchers is the need to create understandable educational resources to inform participants that reinforce state-of-the-science about cerebral amyloid, including uncertainties about its exact role in the AD process. Further, these resources need to be presented repeatedly until AD health literacy is reinforced to a minimal level and AD health fluency can be demonstrated. Health literacy is a stronger predictor of objective health than age, income, employment, education and race [67]. Literacy promotes health status through the adoption of health-related behaviors and the savvy application of health-related knowledge [68].

As a recommendation, we promote a tiered series of health literacy presentations with repeated tests at each level. At the first level is a series of public health statements about AD risk, the amyloid hypothesis, and its possible fallibility. The second level would contain more detailed information about the nuances why amyloid status may not predict future AD status with the degree of certainty needed in medicine. The final level of health literacy education concretizes that there are many risk factors for AD. We envision the creation of a personalized risk profile that details all known risk factors for AD. In this way the research

participant could personalize the medical relevance of his/her amyloid status within a larger picture of known risk and protective factors.

Finally, investigators need to consider the impact disclosure may have on the validity of their results. For example, disclosure of APOE e4 carrier status had an impact on cognitive performance on psychometric tests in one recent study, suggesting that risk results may impact study outcomes [69]. In natural history studies for which life-long participation is a realistic possibility or goal, this may require case-by-case examination.

Research may provide the safest setting for disclosure. With the FDA approval and widespread availability of amyloid imaging, participants will likely have access to commercial testing in for-profit diagnostic facilities, similar to genetic testing such as APOE. In contrast to this fee-for-service option, the research interaction would be highly regulated, both by local Institutional Review Boards and by national bodies such as the FDA (in the setting of drug trials). To the extent that these regulations ensure that results (both positive and negative) are delivered by adequately trained and skilled professionals with experience in delivering similar information, this setting may minimize the likelihood of catastrophic reactions. Moreover, the interaction should include highly skilled investigators, well versed in the level of current knowledge related to scan findings.

Conclusions

In summary, we conclude that the clinical use of amyloid PET in cognitively normal persons is premature at this point. Further understanding of the implications of scan results is needed to adequately instruct the clinical interaction and the information provided. To achieve this level of understanding, research is needed. In the research setting, we conclude disclosure is possible. The dichotomy between these recommendations may, in and of themselves, raise an ethical question. Is it appropriate to treat patients and research participants differently? We believe it is. The basis for this difference is (1) the requirement for evidence-based clinical utility before widespread use can be recommended; and (2) that the knowledge gained through research, in our opinion, shifts the risk/benefit balance toward offering disclosure in this setting.

In effect, these recommendations are not new. Participants should be treated with respect, beneficence, and justice. We do not advocate that every cognitively normal research participant should learn their amyloid status, but we assert that we should not keep information from those persons who are so vital to our common goal of preventing AD.

Acknowledgments

JDG receives research support from the National Institutes of Health (AG016570), the Alzheimer's Association (NIRG-12-242511), the John Douglas French Foundation, and the Sidell-Kagan Foundation. He has served as consultant to Avanir and Phloronol; and serves as site investigator for clinical trials sponsored by Elan, Genentech, Janssen Alzheimer Immunotherapy, Bristol-Myers Squibb, Pfizer, and the Alzheimer's Disease Cooperative Study (ADCS).

DKJ receives research support from the National Institutes of Health (R01AG09009, R01AG033673, P30AG035982) and the Michael J. Fox Foundation.

JMB receives research support from the National Institutes of Health (R01AG034614, R01AG03367, P30AG035982, U10NS077356, UL1TR000001). He has received royalties from publishing Early Diagnosis and Treatment of Mild Cognitive Impairment (Wiley Press, 2008) and *Dementia: An Atlas of Investigation and Diagnosis* (Clinical Publishing, Oxford, England, 2007); has served on the Novartis speakers' bureau and as a consultant for PRA International; and receives research support from Jannsen, Wyeth, Danone, Pfizer and Baxter.

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Future Perspective

Amyloid imaging is positioned to change the landscape of AD research. Enrollment of cognitively normal participants at increased risk for AD will be greatly facilitated and this may accelerate AD research. With new studies utilizing amyloid imaging technology, parallel research on the implications of learning amyloid results in cognitively normal populations will ensure that research conduct is ethical and safe.

Executive Summary

- Amyloid PET imaging represents an advance in AD biomarkers that will facilitate research into the earliest stages of AD
- Clinical use of amyloid PET in cognitively normal patients is not justified
- Research disclosure of amyloid PET results to volunteers is debated and not widely practiced
- The psychological and behavioral impact of research disclosure of amyloid status to cognitively normal participants is currently unknown
- Research guidelines emphasize the autonomy of participants and studies suggest that AD risk information can be shared with minimal psychological harm
- When performed, research disclosure of amyloid PET status requires steps to ensure truly informed consent, education to ensure health literacy, careful monitoring of patient outcomes associated with disclosure, and provision of counseling and medical resources as necessary