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Journal
Neurodegenerative Disease Management, 3(3)

ISSN
1758-2024

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Publication Date
2013-06-01

DOI
10.2217/nmt.13.25

Peer reviewed

HHS Public Access

Author manuscript

Neurodegener Dis Manag. Author manuscript; available in PMC 2015 July 10.

Published in final edited form as:

Neurodegener Dis Manag. 2013 ; 3(3): 219–229. doi:10.2217/nmt.13.25.

Amyloid imaging, risk disclosure and Alzheimer's disease: ethical and practical issues

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SUMMARY

PET ligands that bind with high specificity to amyloid plaques represent a major breakthrough in Alzheimer's disease (AD) research. Amyloid neuroimaging is now approved by the US FDA to aid in the diagnosis of AD, and is being used to identify amyloid-positive but asymptomatic individuals for secondary AD prevention trials. The use of amyloid neuroimaging in preclinical populations raises important ethical and practical challenges, including determining appropriate uses of this technology, evaluating the potential benefits and harms of disclosing results, and communicating effectively about testing with patients and family members. Emerging policy issues also require consideration (e.g., legal safeguards for biomarker-positive individuals). Further research is needed to inform effective and ethical implementation and regulation of amyloid imaging.

The post-mortem diagnosis of Alzheimer's disease (AD) is based on neuropathological grading of the burden and topographic distribution of two characteristic lesions: amyloid plaques composed of aggregated forms of the amyloid-β (Aβ) polypeptide; and neurofibrillary tangles (NFTs) composed of aggregated hyperphosphorylated tau protein [1]. Until recently, the presence of amyloid plaques and NFTs could not be confirmed during the patient's life, and the antemortem diagnosis of AD was made based on clinical criteria and

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Financial & competing interests disclosure

JS Roberts' work is supported by the University of Michigan Alzheimer's Disease Center and National Human Genome Research Institute grants R01 HG02213 (Risk Evaluation and Education for Alzheimer's Disease) and R01 HG05092 (Impact of Personal Genomics). JS Roberts has consulted in the past for Eli Lilly as part of a Bioethics Advisory Board addressing the potential uses of amyloid imaging in clinical practice. He has no current financial involvement with Eli Lilly. GD Rabinovici is supported by the following: National Institute on Aging K23-AG031861; Alzheimer's Association IIRG 203723, Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly); the John Douglas French Alzheimer's Foundation; and the Hellman Family Foundation. GD Rabinovici has consulted for Eli Lilly and receives research support from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), the manufacturer of the amyloid PET ligand florbetapir. LB Dunn has consulted in the past for Eli Lilly as part of a Bioethics Advisory Board addressing the potential uses of amyloid imaging in clinical practice. She has no current financial involvement with Eli Lilly. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

the exclusion of other potential causes of cognitive decline using laboratory testing and structural neuroimaging [2]. This approach has significant limitations, as the clinical diagnosis of AD (even when made by specialized clinicians) has been found to have only limited sensitivity and specificity when compared with autopsy, particularly in early stages of the disease [3]. Therefore, an important goal of recent AD research has been to develop biological markers that can detect amyloid plaques and NFTs during a patient's life.

Development of amyloid imaging

A major breakthrough in this effort has been the development of PET ligands that bind to amyloid plaques with high specificity, particularly to the neuritic forms of plaques (NPs) that are most closely associated with neuronal injury [1]. The first amyloid PET ligand to be successfully applied in human studies was carbon-11-labeled Pittsburgh compound-B (PIB) [4]. PIB has high affinity for the fibrillar Aβ found in NPs in post-mortem brain samples, and *in vivo* studies demonstrate high PIB binding in AD patients compared with normal controls in brain areas known to be rich in NPs [4,5]. Post-mortem studies of individuals imaged with PIB-PET during their life confirm strong correlations between *in vivo* PET signal and the distribution and burden of NPs found post-mortem [6,7].

PIB was rapidly embraced by the research community, but has limited potential as a clinical diagnostic tool, given the very short half-life of carbon-11 (20 min). In subsequent years, four amyloid imaging agents labeled with F^{18} (110 min half-life) have been developed for clinical use. Similarly to PIB, the F18-labeled amyloid tracers bind to NPs *in vitro*, show high cortical binding in AD patients and most have been validated compared with post-mortem measures of Aβ [8–11]. In April 2012, the US FDA approved the use of one of these agents, florbetapir (Amyvid™; Eli Lilly and Company, IN, USA) for "PET imaging of the brain to estimate Aβ NP density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline" [101]. A similar recommendation by the European Medicine Agency's Committee for Medicinal Products followed in October 2012 [102]. In new diagnostic criteria, amyloid PET findings can be applied in conjunction with a clinical assessment to increase the certainty that AD pathophysiology is the cause of mild cognitive impairment (MCI) or dementia [12–14]. Recently, an Amyloid Imaging Task Force commissioned by the Society for Nuclear Medicine and Molecular Imaging and the Alzheimer's Association established appropriate use-criteria for this technology, recommending that amyloid PET should be used only in addition to a comprehensive clinical evaluation by a dementia expert, and given its high cost, use should be limited to patients in whom there is significant clinical uncertainty about the etiology of cognitive impairment (specifically, patients who present with persistent and unexplained MCI, atypical symptoms and/or an early age of onset) [15]. Amyloid PET is not yet reimbursed in the USA by third-party payers, who have requested additional data demonstrating that scan results impact clinical care and patient-based outcomes.

Amyloid PET has several important limitations. For one, the technique only detects one of the two core pathologic features of AD. Although required for the pathologic diagnosis of AD and correlated more strongly with cognitive symptoms in AD than amyloid plaques, NFTs are not detected by Aβ PET tracers [16]. In addition, Aβ aggregates are not specific to

AD; amyloid plaques are frequently found in dementia with Lewy bodies, the second most common degenerative dementia, as well as in blood vessels in cerebral amyloid angiopathy. Therefore, individuals with these conditions show high signal on amyloid PET scans in patterns similar to those seen in AD [7,17,18]. Efforts are ongoing to develop PET tracers that selectively bind to aggregated forms of tau in NFTs [19,20] Combined amyloid and tau imaging would more accurately capture the molecular diagnosis of AD and, thus, greatly enhance diagnostic specificity. An additional limitation of amyloid PET as an AD diagnostic tool is that, in most studies, 20–40% of cognitively normal individuals (NCs) show high tracer binding [21]. The prevalence of amyloid positivity in NCs is age dependent (ranging from ~5% in individuals aged 50 years to 50% or more in persons older than 80 years) and correlates highly with the presence of *APOE* ε4, the major genetic risk factor for sporadic AD [22–24].

Amyloid imaging in asymptomatic individuals

Converging data from multiple centers show that $A\beta^+$ asymptomatic individuals already show 'AD-like' changes in brain structure and function [25–27]. When followed longitudinally, $A\beta^+$ NCs demonstrate greater decline in memory and other cognitive domains, and accelerated brain atrophy as compared with $A\beta^-$ persons [28–31]. These data, consistent with similar data based on cerebrospinal fluid biomarkers of AD pathology, have led to the evolving concept of 'preclinical AD'. Here, $A\beta^+$ deposition is an early event in a pathophysiological cascade that includes neurofibrillary pathology, inflammation, synaptic dysfunction, neuronal loss and, ultimately, cognitive decline and dementia [32]. Prospective cohort studies, such as the AIBL project, suggest that the AD cascade takes place over decades, and that Aβ deposition may precede even mild clinical symptoms by 15 years or more [33,34]. This model is supported by evidence from carriers of autosomal dominant mutations that cause familial AD, who show evidence of amyloid deposition prior to other types of neurodegeneration and many years before the expected onset of symptoms [35,36]. The long preclinical phase of AD has been viewed as a potential therapeutic window in which anti-amyloid therapies might be initiated before irreversible end-organ damage has occurred [32,37]. Indeed, secondary prevention clinical trials of amyloid-directed therapy in asymptomatic individuals are now being launched; two in familial AD and one (the 'A4' trial) in NCs who are found to be $A\beta^+$ by PET imaging [38–40].

Use of amyloid imaging in clinical trials and clinical practice has raised questions about whether – and to whom – scan results should be disclosed. For the many years that amyloid PET was limited to research studies, results were typically not disclosed to participants (regardless of whether they were cognitively impaired or not) since the accuracy of the technique was under active investigation. The FDA approval of florbetapir has changed the landscape in this regard, as the scan is now accessible to cognitively impaired patients in the clinic, and it is likely that, moving forward, many research studies will elect to disclose results to participants. For example, in the aforementioned A4 trial, a positive amyloid PET scan is an inclusion criterion, and an individual's Aβ status will be disclosed as part of the informed consent procedure [40]. Meanwhile, a recent survey of neurologists specializing in dementia care suggested that a notable minority (24%) would consider clinical use of amyloid imaging for screening of asymptomatic individuals [41].

The value of such uses of amyloid imaging are unknown and highly debated. A positive amyloid PET scan at baseline is indeed associated with an increased risk of future, clinically significant cognitive decline, defined as 'conversion' from normal to a diagnosis of MCI or AD dementia [42,43]. However, the number of prospective studies is still small, and the relative risk associated with $A\beta^+$ for the future evolution of dementia is yet to be estimated with precision (if aforementioned efforts to image NFTs are successful, combined Aβ and tau PET data would probably enhance prognostic power in this area). Given such limitations, the Amyloid Imaging Task Force specifically recommended against the clinical use of amyloid PET in asymptomatic individuals, reasoning that "there is significant potential for patients and families to make inaccurate assumptions about risk and future outcomes on the basis of amyloid PET results. Currently the potential harms outweigh the minimal benefits" [15].

Of course, the extent that such speculations about possible benefits and harms are borne out in the real world is unknown. The prospect of disclosing amyloid imaging results and related AD risk information to asymptomatic individuals raises numerous challenges, necessitating in-depth empirical research and consideration of ethical dilemmas. This need is particularly urgent as this technology is already being deployed in new contexts, such as AD prevention trials. Below, we discuss some of the key questions and controversies surrounding the disclosure of amyloid imaging results to asymptomatic individuals.

Current questions & controversies

How does disclosure of amyloid imaging results to asymptomatic individuals compare & contrast to disclosure of predictive genetic test results?

Many of the ethical and practical dilemmas raised by amyloid imaging have been faced before in the context of genetic testing for AD. For example, in the 1990s, the identification of genetic variants associated with a higher risk of AD (e.g., presenilin mutations for familial AD and the *APOE* ε4 allele for sporadic AD) sparked much debate about the appropriate uses of predictive testing for AD, as well as research on the psychological and behavioral impact of testing [44,45]. Given its high predictive value, genetic testing for rare familial forms of AD has been incorporated into clinical practice, whereas *APOE* genotyping is generally discouraged in asymptomatic individuals [46]. However, given the relatively high prevalence of ε4 alleles in the general population, *APOE* testing is often of interest to relatives of AD patients, as well as to clinical researchers seeking 'enriched' populations for prevention trials [47].

However, *APOE* genetic testing differs from amyloid imaging in several important ways (Table 1). One involves the degree of certainty versus ambiguity in the test result itself. In the case of *APOE* genetic testing, an individuals' test results yields 0, 1 or 2 copies of the ε4 risk allele. Risk of AD increases with the number of copies of the ε4 allele, and scores of studies have examined the degree of increased risk conferred with each detected risk allele. By contrast, prospective longitudinal data regarding the predictive value of a positive amyloid scan in NCs are much more limited. Furthermore, while the FDA has mandated a binary visual read of amyloid scans as 'positive' or 'negative' in clinical practice [8], when tracer binding is expressed as a continuous measure, 'intermediate' results of unclear

significance are found in up to 20% of subjects [48]. Even in those clearly in the positive range, it is not clear whether higher amyloid burden is associated with higher risk or more imminent decline, and the significance of the spatial distribution of amyloid found in the brain is also not known [8,49].

Amyloid imaging results also differ from genetic test results with regard to temporal issues, such as the time in the life course where testing might be pursued (e.g., mid-life vs older adulthood), as well as the imminence of risk information conferred by test results. For example, an amyloid-positive imaging result could be associated with more imminent disease risk than a positive genetic test result (e.g., within the next few years vs at some point in one's lifetime), although the precise timeframe for conversion probably depends on numerous other variables that are not currently well defined for predictive purposes. The implications of a positive amyloid imaging result for immediate family members are also not entirely clear at this point, whereas positive genetic results imply a potential risk for genetically related individuals. In addition, amyloid imaging assesses a dynamic process, where repeat testing could yield different results over time. Conversely, genotype status is fixed at birth and does not change.

The different types of information generated by these distinct modes of assessment might also have implications for how patients and family members use, make sense of and react to test results. The power of imaging as a modality needs to be considered here. The knowledge that one has amyloid in one's head – viewable in images as 'growing' in the brain – might trigger different cognitive, emotional and behavioral reactions as compared with the more abstract knowledge of one's genotype. The former may be experienced as more 'real' and threatening, with individuals and family members biased to misinterpret a positive imaging test result as meaning that the patient already has or is developing AD, as opposed to viewing the test result as just one of several risk factors. However, to our knowledge, empirical studies have not yet examined whether reactions to imaging versus genetic test results actually differ. Such research could help guide efforts to provide appropriate pre- and post-test education and counseling.

What are the potential benefits & harms in disclosing results to asymptomatic individuals?

The decision whether or not to disclose amyloid imaging results represents a classic ethical tension often involved in the application of emerging medical technologies. On one hand, arguments emphasizing patient autonomy might suggest that access to information regarding one's brain health is an individual's right, and that researchers and clinicians would be upholding values of transparency and truth telling by disclosing scan results. However, at present, consensus within the medical community is against disclosure, justified by the principle of non-maleficence (i.e., avoiding potential harms of disclosure given the currently unproven clinical utility of imaging in this context). From a public health perspective, the precautionary principle would further suggest that a policy restricting disclosure of results is just, because it protects both individuals and society from reasonably suspected harms (e.g., undue distress in patients and family members, and unnecessary use of healthcare resources). This view would hold that strict regulation of practice in this area is appropriate

until scientific knowledge has established that the procedure in question is indeed not harmful, or at least that the benefits of disclosure are proven to outweigh the harms.

However, although disclosure of amyloid imaging results to asymptomatic individuals is not currently advisable in clinical practice, one can imagine a future where this practice might be useful. Assuming progress in the aforementioned efforts to find effective secondary prevention measures for AD, patients would theoretically be able to use amyloid imaging results to inform their healthcare decisions. Options might not only include medications, but also health behaviors suggested by the emerging evidence for modifiable risk and protective factors involved in AD and related dementias [50]. One could even make the case that improved AD treatments need not be available to warrant access to one's amyloid imaging results in certain scenarios. National survey data suggest that a significant proportion of the US adult population is interested in learning more about their risk of AD and willing to pay substantial fees for this information [51]. Studies of asymptomatic individuals who have undergone AD risk disclosure, with disclosure of their *APOE* genotype status, suggest they have found it useful for a variety of reasons, including informing advance planning, encouraging monitoring of AD treatment and research, gaining psychological relief (in the case of negative test results) and satisfying a perceived need for risk information [52,53]. These studies, a series of randomized clinical trials collectively known as the REVEAL study, further suggest that adverse psychological responses to risk information (even ε4-positive results), such as clinically significant depression or anxiety, are generally rare and transient when results are delivered by trained clinicians in the context of a genetic education and counseling protocol [54]. Given these data, some would argue that withholding amyloid imaging results, particularly if obtained in the context of clinical research, could be unduly paternalistic [55]. In addition, a recent survey of over 150 investigators in the large-scale Alzheimer's Disease Neuroimaging Initiative found that a majority were in favor of returning research results to both participants with MCI (73% endorsing) and NCs (58% endorsing) [Shulman MB *et al*. A survey of ADNI investigators (2013), Submitted]. Some respondents qualified their assertions by stating that the disclosure should only occur in the context of a separate research study designed to help understand the process and impact of communicating amyloid imaging results.

Of course, there are many reasons why experts in the field have misgivings about disclosing amyloid imaging results, particularly to NCs. Given the early state of research in this area, some contend that not enough is known about the relationship between amyloid status and AD risk to warrant disclosure [56]. There are also potential psychological risks involved in disclosing imminent risk information for a severe and incurable disease such as AD. Although the REVEAL data regarding psychological adjustment to test results are encouraging, group mean data may not apply to a given individual case; furthermore, the study involved mostly well-educated participants who were screened at baseline for suicidal ideation, and severe levels of depression and anxiety, limiting the generalizability of results [57]. Adverse psychological outcomes may be more likely if individuals misinterpret test results (e.g., taking an amyloid-positive result to mean that one is destined to develop AD), thus, underscoring the importance of patient education. Another type of risk entailed by disclosure of amyloid status is social stigma, whereby individuals could encounter

discrimination in the workplace or insurance market [37]. Federal and state antidiscrimination laws (e.g., the Genetic Information Nondiscrimination Act) have been developed around the use of predictive genetic testing [58], but these protections may not apply to biomarker-positive individuals. The policy domain of most relevance here may be the long-term care (LTC) insurance market, where AD accounts for a significant proportion of LTC costs and the Genetic Information Nondiscrimination Act does not apply [59].

Communication of imaging results: who, what & how?

Should a clinician or researcher decide that disclosure of amyloid imaging results is appropriate, many challenges are associated with the actual conveying of this information. Given the complexities and nuances involved, disclosure is best left to trained professionals, who are not only knowledgeable about amyloid imaging and the available AD risk literature, but also skilled in health education and risk communication. A prominent challenge lies in deciding exactly what to communicate to patients and family members about imaging findings and related AD risk information. With regard to the imaging results themselves, as noted earlier, the FDA has mandated a visual read of amyloid scans as 'positive' or 'negative' in clinical practice [8]; however, research studies have found 'intermediate' results of unclear significance in up to 20% of subjects [48]. Thus, framing test results in binary terms may not be fully accurate, and clinicians may need to prepare patients to receive unsatisfyingly ambiguous results. As for incorporating imaging results into estimates of AD risk, the ideal would be to provide a quantitative estimate. Yet there have been only a limited number of prospective longitudinal imaging studies that follow the progression of NCs. The largest published study estimated that a positive amyloid scan in older NCs is associated with a hazard ratio of 4.85 for progressing to clinically significant cognitive impairment[43]. However, this estimate was based on longitudinal decline in 23 out of 150 individuals, and only nine individuals were diagnosed with AD dementia. Clearly, more data are needed to provide reliable quantitative estimates of AD risk based on Aβ status.

Even when quantitative estimates are available, conveying this information can be challenging for providers, who may not be schooled in state-of-the-art risk communication techniques, including use of natural frequencies (vs percentages); supplementation of verbal communications with visual aids (e.g., pictographs) and take-home education materials to reinforce risk messages; and provision of resources to assist coping with risk status [60–62]. A survey of neurologists regarding their usual practices in disclosing diagnoses of MCI found that many of these strategies were not routinely utilized[63], suggesting a need for greater dissemination of best practices in risk communication via continuing education offerings and web-based toolkits. Even in best-case scenarios, however, patients will not always interpret or recall risk information as experts might desire. Findings from the REVEAL trials suggest that, although most participants got the gist of the take-home risk messages (i.e., they knew whether or not their results indicated elevated risk and that results were not definitive), many could not recall the specifics of their results and/or did not take risk estimates at face value [64,65]. Such results suggest the need for humility on the part of providers regarding both the achievable goals of patient education and the precision with which risk estimation can be provided. Even with our impressive technological tools, there

is only so much that can be said with certainty regarding prognosis for a highly complex, multifactorial neurological disease.

Future perspective

Policy & practice

Humility is also important when trying to project future trends for a rapidly evolving field spanning numerous disciplines and domains. Yet it seems safe to say that key policy issues are emerging that will help determine future access to, and provision of, amyloid imaging within the US healthcare system. Later this year, the Centers for Medicare and Medicaid Services are expected to rule on whether Medicare will cover the use of amyloid imaging agents in the diagnosis of dementia. Given the limited amount of current evidence for its clinical utility in improving diagnostic accuracy, let alone affecting patient outcomes [103], it seems likely that insurance coverage of this technique will not be forthcoming in the near future. Indeed, on 31 January 2013, a Centers for Medicare and Medicaid Services advisory committee voted against coverage, over the objections of prominent advocacy and professional organizations, including the Alzheimer's Association and Society of Nuclear Medicine and Molecular Imaging [104]. Given the high cost (US$3000–6000), and highly specialized technology and personnel required for this type of imaging (contrast this to *APOE* genotyping, which can now be obtained direct to consumer for under $100) [105], overall use in the USA is likely to remain quite limited until insurers agree to cover this service.

In the meantime, one area of health policy that may deserve greater attention involves legal protections for biomarker-positive individuals[37]. A review by Klunk suggests that approximately a quarter of older NCs would be found to be $A\beta^+$ if scanned [66]. The rising prevalence of older adults in the USA and the continued development of a range of AD biomarkers may ultimately encourage insurers, particularly those in the LTC industry, to use biomarker information to actuarially justify denial of coverage or increased premiums. Although such actions would be both legal and logical on the part of LTC insurers, they would seem to unjustly punish individuals whose at-risk status was no fault of their own. It may, therefore, be advisable to develop policies that address the potential use of biomarkers by LTC insurers such that biomarker-positive individuals are not unfairly priced out of this market.

Research agenda

There are certainly many needs and directions for future research in this area (given space limitations, we focus in this section on clinical and public health research). Obviously, large prospective longitudinal studies with diverse populations will be required to gain a clearer understanding of the predictive validity of amyloid imaging for AD and related dementias. Risk modeling in AD will ultimately need to integrate amyloid imaging data with other established and emerging risk and protective factors, including biological, demographic and psychosocial factors[67]. Once predictive capabilities have been enhanced, research demonstrating the clinical utility of amyloid imaging will be needed. Recommendations from a recent white paper from the Institute for Clinical and Economic Review (ICER) are

highly instructive here [103]. To classify existing studies and identify future needs, the ICER policy development group used a hierarchy of studies across the levels of technical efficacy, diagnostic accuracy, diagnostic impression, diagnostic action, patient and societal outcomes. Their review found that only five level 3 studies had been conducted, with none across levels 4–6, pointing out clear study needs at these higher levels (Table 2). Although this framework was developed with diagnostic testing in mind, it could easily be adapted to guide studies of predictive testing.

Given the numerous ethical, legal, educational and social issues raised by the use of AD biomarkers, it would also be important to begin to generate a body of evidence in the social and behavioral sciences to support safe, ethically sound and clinically effective implementation. For example, research would be helpful in the following ways:

- Identifying proven education strategies for disclosing imaging results, aided by a greater appreciation of how patients and family members make sense of test findings;
- Understanding the psychological and behavioral effects of test results on patients and families, including the extent and likelihood of adverse emotional reactions to positive scan results, as well as health behavior changes prompted by test information;
- Exploring policy implications of the more widespread use of AD biomarkers.

Such empirical studies would probably provide more information not only in the AD field, but also for addressing challenges in the development of other emerging biotechnologies that attempt to identify preclinical populations for the purposes of disease prevention and risk reduction.

In conclusion, amyloid imaging represents a promising new technology with the potential to improve diagnostic accuracy in AD and perhaps, ultimately, to screen asymptomatic individuals. Given the complexity involved in interpreting test results, however, it will be critical to make sure that efforts in patient and provider education and health policy keep pace with technological advances and treatment developments in the field. In particular, methods of discussing and disclosing amyloid imaging results require significant attention. A focus on the training and continued education of both dementia care providers and nonspecialists on this topic is warranted, as well as collaborations involving allied health professionals with expertise in patient education/counseling and experience at the intersection of illness and mental health (e.g., psychologists, social workers and psychiatrists). These partnerships would provide a foundation for developing best practices and professional guidelines for pretest counseling sessions, post-test disclosure procedures and longer-term follow-up. Such practices should be evidence-based to the extent possible (drawing upon the research agenda described above), as well as tailored to the individual's and family's unique needs. Education and counseling might include, for instance, discussion of possible psychological and behavioral responses to results, potential implications for family members, legal and financial issues (e.g., insurance), and provision of resources or referrals to assist with coping. Careful attention to these issues is not only ethically imperative, but also signals to patients and families that this test may warrant more

forethought than routine medical tests given its important, potentially unforeseeable implications and risks.

Acknowledgments

The authors gratefully acknowledge L Le for her assistance with manuscript preparation.

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▪ of interest

▪ ▪ of considerable interest

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Practice Points

- Emerging neuroimaging technologies now allow for *in vivo* detection of amyloid plaques that may be involved in the pathophysiology of Alzheimer's disease (AD) and related dementias.
- Although amyloid imaging currently has many significant limitations, it has been approved for clinical use in symptomatic patients and is being used to identify at-risk participants in AD prevention trials.
- The decision whether – and to whom – to disclose amyloid imaging results raises several ethical and practical issues.
- Similar issues have been encountered previously in predictive genetic testing for AD, but amyloid imaging poses distinct challenges given the nature of the information provided.
- Disclosing amyloid imaging results to asymptomatic individuals is not currently recommended given its lack of proven clinical utility and the potential harms, including undue psychological distress and misinterpretation of scan results.
- Imaging of asymptomatic individuals may become more advisable over time, with advances in AD treatment options and improvements in the predictive value of testing.
- Disclosure of imaging results should incorporate best practices in risk communication and may necessitate policy changes to protect biomarker-positive individuals against insurance discrimination.
- Social and behavioral research is needed to help identify the extent and likelihood of clinical and psychosocial benefits and harms involved in the disclosure of amyloid imaging results.

Table 1

Comparison of genetic susceptibility testing (using *APOE* genotyping) versus amyloid imaging in asymptomatic individuals.

Test characteristic	Genetic susceptibility testing	Amyloid imaging
Approved for clinical use	Consensus statements recommend against use	Approved in 2012 by the US FDA for help in diagnosing AD, but not for risk assessment
Range of possible test results	Six *APOE* genotypes (ε2/ε2; ε2/ε3; ε2/ε4; ε3/ε3; ε3/ε4; ε4/ε4); ε4 status: 0, 1 or 2 alleles	Typically positive or negative (as the FDA mandates a binary read); continuous results are potentially available, but the significance is currently unclear, inconclusive results are possible
Stability of test results	Fixed, does not change over time	May convert from negative to positive over time
Timing of test seeking	Could be conducted anytime in adulthood	Most likely to be conducted in mid-to-late life
Imminence of risk information yielded	Risk of clinical AD at some point in one's lifetime	Risk of clinical AD probably within next 10–15 years
Predictive value	Low to moderate	Under active investigation
Implications for family members	Carrier status has implications for blood relatives	Unclear
Cost/insurance coverage	As low as US$99 (via DTC genetic testing services). Not reimbursed by Medicare or other insurance	$3000–6000. Not currently covered by Medicare or other insurance
Legal safeguards	Federal GINA law and various state laws protect against some (not all) forms of genetic discrimination	No legal safeguards for positive test results beyond existing laws

AD: Alzheimer's disease; DTC: Direct to consumer; GINA: Genetic Information Nondiscrimination Act.

Table 2

Existing number of studies of diagnostic testing for Alzheimer's disease.

Study level	Studies (n)
1: technical efficacy	17
2: diagnostic accuracy	553
3: diagnostic impression	5
4: diagnostic action	None
5: patient outcomes	None
6: societal outcomes	None

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