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PERSPECTIVE

Disclosure of preclinical Alzheimer's disease biomarker results in research and clinical settings: Why, how, and what we still need to know

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Abstract

Disclosure of personal disease-related information to asymptomatic adults has been debated over the last century in medicine and research. Recently, Alzheimer's disease (AD) has been conceptualized as a continuum that begins with a "preclinical" stage in which biomarkers are present in the absence of cognitive impairment. Studies have begun assessing the safety, psychological, and behavioral effects of disclosing both AD-related genetic and biomarker information to cognitively unimpaired older adults. Yet, debate continues over the appropriate circumstances and methods for returning such information. This article outlines concerns with and rationale for AD biomarker disclosure and summarizes findings from prior studies. Overall, this article aims to describe and respond to key questions concerning disclosure of amyloid positron emission tomography scan results to asymptomatic adults in a research setting. Moving forward, such conditions are important to consider as interventions target the preclinical phase of AD and normalize disclosing biomarker information to cognitively unimpaired persons.

KEYWORDS
Alzheimer's disease, amyloid positron emission tomography, disclosure, future directions, personal impact, research impact

1 | INTRODUCTION

Momentum in revealing personally relevant disease-related genetic and biomarker information is mounting, particularly within the context of Alzheimer's disease (AD). In the 2000s, studies disclosed genetic test results in the form of apolipoprotein (*APOE*) ε4 carrier status to cognitively unimpaired research participants with a first-degree relative with AD dementia (for systematic review see Bemelmans et al.[1]). Recent advancements in tracking the pathophysiological progression of AD allow researchers to identify characteristic brain changes (i.e., amyloid beta [Aβ] plaques, neurofibrillary tau tangles) before AD symptoms develop. Studies demonstrate that the presence of brain markers such as Aβ is more predictive of cognitive decline than *APOE* ε4 alone.[2] Therefore, biomarker information may be more useful in determining AD dementia risk than *APOE* ε4 carrier status.

The 2018 National Institute on Aging–Alzheimer's Association (NIA-AA) research framework proposed defining AD using biomarkers of pathophysiology, including Aβ protein (A), tau protein (T), and

neurodegeneration (N), rather than clinical symptoms alone.[3] Using the ATN research framework, an individual without cognitive decline, but with elevated markers of Aβ has AD pathologic change and is on the AD continuum. Aβ predicts subsequent cognitive decline in cognitively normal adults.[2,4] Given that Aβ is a hallmark of AD pathophysiology and is related to cognitive decline, it is the target of many investigational treatments and has been the focus of AD biomarker disclosure.[5] Aβ accumulation is a necessary part of the pathological progression to AD dementia. Its presence has implications for an individual's AD dementia risk and potentially should be shared with those individuals.

The purpose of this article is to review the rationale for disclosure of AD genetic and biomarker results to asymptomatic adults within the context of research and clinical settings. We start by examining the rationale for disclosure in research settings by considering the balance of potential risks and benefits to the research community. We then review the current practices of Aβ positron emission tomography (PET) disclosure in research settings and describe existing knowledge gaps. As the rationale and concerns may differ by context, we next consider the rationale for disclosure of Aβ PET results in clinical settings along with knowledge gaps and ongoing research to determine clinical validity and utility. Last, we provide recommendations for future research in AD biomarker disclosure to cognitively unimpaired research participants.

RESEARCH IN CONTEXT

1. **Literature Review**: A literature review was conducted using the PubMed database and resulted in a total of 45 articles that were reviewed for the purposes of this paper. There are limited studies that have disclosed amyloid beta (Aβ) positron emission tomography (PET) results to cognitively unimpaired research participants. More information is still needed on the best practices and impact of disclosing such information.
2. **Interpretation**: We critically assessed the field of preclinical Alzheimer's disease (AD) biomarker disclosure through a research and clinical lens. Based on current understanding of AD biomarkers and findings from previous studies disclosing AD biomarkers to cognitively unimpaired research participants, Aβ PET results can be safely and accurately shared with participants.
3. **Future Directions**: This article recommends considerations for developing a biomarker disclosure protocol focusing on three main themes: participant understanding of the study, effective communication of results, and participant safety. Future studies are needed to further understand the personal utility of Aβ information, disclosure best practices, longer term psychosocial impacts, and the effect of disclosure on trust in medical research.

2 | DISCLOSURE OF AD BIOMARKER RESULTS IN RESEARCH SETTINGS—WHY?

Decisions regarding disclosure of AD risk-related information to research participants without clinical symptoms depends on the balance of risks and benefits. Aβ PET scan results have most commonly been provided to research participants within the context of clinical trials in which elevated Aβ is an eligibility requirement for participation. In pursuit of upholding transparency and ensuring informed consent, providing Aβ results to these potential clinical trial participants is considered ethically necessary.[6] Growing interest from researchers and research participants coupled with frequency of Aβ PET scans in non-clinical trial research has expanded the potential appropriate circumstances to share Aβ results outside of a clinical trial setting.[7,8]

The most common reasons AD researchers give for desiring to disclose AD biomarker results include improving transparency and trust in medical research studies, which in turn leads to improved participant recruitment, engagement, and retention.[7] Improved transparency between research institutes and communities may be particularly important for expanding research to include more individuals from underrepresented groups (URGs). For example, prior research with Black respondents suggests that perceived benefit, minimal risk, trust, information dissemination, and reduced fear may be associated with increased likelihood to participate in an AD prevention trial or undergo cognitive screening.[9,10] A study surveying investigators from the Alzheimer's Disease Neuroimaging Initiative (ADNI) reported that a majority of investigators were interested in disclosing Aβ PET results to cognitively unimpaired participants. Investigators emphasized a need for guidance on how to provide these results and for research to assess both the value and impact of returning results on study validity and participant well-being.[7] A focus group study conducted in Belgium similarly found that researchers generally were in favor of Aβ PET disclosure in various hypothetical scenarios.[11]

Several studies have consistently shown that the risk for psychological harm (e.g., depression, anxiety, suicidality) related to disclosure of AD genetic or biomarker results to cognitively healthy adults is low.[5] Studies disclosing *APOE* ε4 carrier status to cognitively unimpaired research participants found no significant short-term psychological symptoms on measures of depression and anxiety.[12] In a small sample (n = 11) from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study, Lim et al. reported that participants with non-elevated Aβ PET scan results reported relief, while participants with elevated Aβ felt anxious but unsurprised.[13] Results suggested that disclosure did not significantly impact individual mood, subjective sense of memory impairment, or perceived risk of developing AD for both groups.[13] In a sample of n = 97 adults enrolled in a physical exercise study at the University of Kansas, Burns et al. reported[14] that participants with elevated Aβ had higher levels of test-related distress compared to those with non-elevated Aβ at 6 weeks and 6 months after disclosure. Although baseline anxiety and depression were associated with total distress at follow-up time points, they reported no statistically

significant group differences in depression or anxiety at any time point between elevated and non-elevated Aβ groups.[14]

In a small subset of individuals who had undergone screening for the A4 study but were ineligible due to non-elevated Aβ results (n = 33), Grill et al. reported that individuals with non-elevated Aβ most commonly reported relief and most participants experienced subclinical distress related to learning the scan results.[15] Similarly, at Keio University in Japan, Wake et al. reported that there were no observable differences between elevated and non-elevated Aβ groups (n = 42) in anxiety, depression, or test-related distress following disclosure.[16] Finally, the largest published study to date (n = 1705; A4 trial) reported no differences in psychological symptoms between elevated and non-elevated groups as measured pre- and post-disclosure (roughly 2–3 months after the disclosure visit).[17]

However, knowledge of *APOE* or Aβ PET scan results may result in short-term increased subjective and objective cognitive decline. For example, *APOE* ε4 carriers with knowledge of their *APOE* status rated their memory more poorly and performed worse on memory tests than ε4 carriers without such knowledge.[18] Conversely, non-carriers with *APOE* knowledge rated their memory more positively than non-carriers without *APOE* knowledge. These results suggest that learning AD-related genetic information may impact subjective memory rating and performance on memory tests. Similarly, individuals who learned their Aβ PET results were elevated reported more frequent subjective memory complaints and concerns that these memory complaints were related to Aβ.[19] Overall, these studies show that disclosure of *APOE* and Aβ PET scan results to cognitively unimpaired research participants can be done safely without immediate psychological harm; however, there may be increased risk of subjective cognitive complaints.

The most common reason participants express interest in receiving their results is a desire to understand their personal dementia risk.[8,20] Although, currently, there is no approved disease-modifying treatment for AD, participants continue to express a desire to know this information. This continued desire suggests participants may still benefit from receiving this information outside of an available treatment. Such benefits may include a better sense of autonomy, planning for the future, or making lifestyle changes.[11,21] In Bunnik et al., the authors claim that without clinical validity, AD biomarker information cannot have personal utility.[22] Such a conservative definition of personal utility neglects the potential benefit participants could experience from receiving AD biomarker information. Prior literature on *APOE* status disclosure found increased long-term care insurance uptake[12] and that participants who learned they were *ε4* carriers were significantly more likely than non-carriers to report AD-specific health behavior change, such as diet, exercise, or medication/vitamins 1 year post-disclosure.[23]

Given behavior changes following *APOE* disclosure, it is likely that participants receiving their biomarker results will similarly make behavior changes. These changes may manifest as healthy lifestyle changes (e.g., exercising, improved diet, etc.) or long-term care planning (e.g., insurance uptake). Supporting this hypothesis, recent findings from the A4 group in the Study of Knowledge and Reactions to Amyloid Testing (SOKRATES) found that individuals with elevated Aβ more often reported thinking about and making health behavior and future plan changes compared to individuals who received a not-elevated result.[19] Disclosing AD biomarker results to participants may motivate long-term care planning, such as selecting a power of attorney or expressing to loved ones a preference to age-in-place, which could reduce the overall projected economic impact of demographic aging in the United States. Receiving Aβ and other biomarker results may allow research participants to develop their own narrative, make healthy lifestyle changes, and plan for the future.

Discussions of AD biomarker disclosure highlight the role of paternalism in research and question the rights of researchers to retain information. While limited and conducted in predominantly White, high socioeconomic status samples, evidence to date suggests that the psychological risk of disclosure is low. Further, disclosure may result in potential benefits to the individual, including bolstered autonomy. Despite not having clear risk predictions for the presence of Aβ, the potential benefits of disclosure outweigh the low risk of self-harm/psychological distress. In the context of the NIA-AA AD research framework, researchers classify participants as having AD regardless of symptom status and many research studies (e.g., clinical trials for secondary prevention of cognitive symptoms) target recruitment of participants based on this designation. To be fully transparent with participants about their disease status and risk for the clinical syndrome, researchers have an obligation to inform interested participants of their biomarker results regardless of symptom status.[24]

3 | DISCLOSURE OF AD BIOMARKER RESULTS IN RESEARCH SETTINGS—HOW?

Lessons in adequately disclosing AD dementia risk status can be drawn from studies disclosing *APOE* status to research participants. Langlois et al.[25] provides a holistic overview of best practices in disclosing *APOE* status within the context of clinical studies by introducing the API Genetic Counseling and Disclosure Process. An interdisciplinary committee developed the process, which includes eight components: requirements of *APOE* testing and reports, psychological readiness assessment, determination of AD risk estimates, guidance for identifying providers of disclosure, pre-disclosure education, *APOE* counseling and disclosure session materials, *APOE* counseling and disclosure session flow, and assessing *APOE* disclosure impact. Standardization of *APOE* disclosure processes promotes participant understanding and better characterization of the impact of disclosure. Best practices from *APOE* disclosure can be leveraged to develop safe and effective AD biomarker protocols.

Already, several AD biomarker disclosure studies in cognitively unimpaired people are underway. To examine results and common practices from these studies, we conducted a review of the literature in the PubMed database using the search term "amyloid disclosure." This search term resulted in 904 results. Titles for the 904 results were reviewed for reference to disclosure of Aβ results, clinical utility of Aβ results, or ethical concerns regarding Aβ disclosure or preclinical dementia. This resulted in a total of 45 articles that were reviewed for the purposes of this paper. A total of 17 articles focused

on symptomatic populations (diagnosis of mild cognitive impairment or dementia); 28 articles discussed implications of Aβ disclosure in asymptomatic or cognitively unimpaired adults (see Table 1 for list).

Table 1 provides a summary of publications on the four Aβ PET disclosure-related studies in cognitively unimpaired older adults. Three of the four studies, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease[26] (A4), Alzheimer's Prevention through Excercise (APEX),[14] and the AIBL,[13] were conducted using a prospective cohort study design. A4, APEX, and the study from Keio University in Japan[16] only included participants 65 and older. AIBL included participants 55 and older. A4, AIBL, and APEX were AD prevention studies (pharmacological and exercise interventions). Within AIBL, disclosure only occurred for participants who expressed interest in learning the results of their Aβ PET scan. The study from Keio University recruited participants from an onsite memory clinic (participants were cognitively unimpaired but may have subjective cognitive decline).

These studies highlight some of the current practices for conducting biomarker disclosure (Table 2), such as including an education/counseling session on possible Aβ PET scan results and their meaning, a psychological screening process to ensure safety of receiving AD-related results, and a separate in-person disclosure session with a results report and time for questions. Additional follow-up after disclosure is also conducted by the studies to assess the impact of disclosure and to monitor psychological symptoms. Overall, biomarker disclosure protocols emphasize adequate screening and monitoring of psychological symptoms to ensure participant safety, to ensure participant understanding of the study and potential risks/benefits, and effective communication of the test result.

To effectively communicate the test result, developing an education session with materials accessible to participants from a variety of backgrounds and education levels is needed. Without accessible educational materials, misinterpretation of results is likely to occur,[27] particularly with regard to a disease as salient in the public consciousness as AD. For example, in the context of receiving AD genetic results in the direct-to-consumer (DTC) marketplace, people are often not properly prepared to understand the meaning of their genetic test results with regard to disease risk and their personal lives and this can result in undue stress.[28] The DTC genetic testing market highlights the need for accessible educational materials, disclosure protocols, and appropriate follow-up with people who choose to learn this information.

To ensure participant understanding of the study, setting expectations up front is important as communicating the limitations of a biomarker result may attenuate interest in receiving the result.[8] For example, it is not recommended to provide granular detail on Aβ burden as there is a lack of empirical data regarding how that information relates to individualized prognoses. Conveying these limitations is challenging, but critical as prior participants have reported desiring more specific risk and degree of elevation information.[29]

Last, in pursuit of focusing on participant well-being, prior studies suggest that participants expect researchers to provide risk-reduction education and follow-up care.[20,30] Moving forward, studies may opt to include lifestyle counseling after disclosure to promote brain health through behavior changes. Participants could be counseled that while they do (or do not) have a biomarker risk factor for AD dementia, they still have self-efficacy in aging healthfully. Vanderschaeghe et al. outline a six-step process that includes recommendations for each of the steps: information, decision, testing, confirmation, return of result, and post-guidance (IDT-CRP).[31] This six-step process can be used in conjunction with the above-mentioned guidance for facilitating safe and effective Aβ PET disclosure to cognitively unimpaired people.

4 | DISCLOSURE OF AD BIOMARKER RESULTS IN RESEARCH SETTINGS—WHAT DO WE STILL NEED TO KNOW?

Using the above-described approach to disclosure, studies to date indicate that disclosure of Aβ PET scan results does not pose short-term psychological risk to cognitively unimpaired research participants. Further studies should continue following up with participants longitudinally to characterize the long-term psychosocial effects of AD biomarker disclosure. Importantly, ongoing Aβ disclosure studies are conducted mostly on at-risk (e.g., participants with a family history of dementia), college-educated, and predominantly White samples. Studies on developing culturally competent disclosure protocols for participants from URGs (e.g., Black, American Indian/Native American, Latine) are needed.

Given that stigma toward those with mild AD appears related to an expected worsening of symptoms, it follows that characterizing risk for decline earlier in the disease would also extend the stigma time frame. This lengthened time frame may cause years of psychological distress related to an anticipated dementia (for a review of concerns regarding stigma in preclinical AD, see Stites[30]). Better characterization of participants sharing results with others can improve our understanding of the impact of this information not just on the individual, but also on those around them. Continued follow-up with participants that have received AD-related genetic and biomarker information can broaden our understanding of how this information is received and its effects on people's lives.

Concurrent with studies characterizing the psychosocial effects of disclosure, advocacy for protections against discrimination will be critical. Discrimination by employers or insurance providers may occur for individuals with personal biomarker knowledge, especially as understanding continues to advance the meaning of biomarkers in the development of AD. Employers and insurance companies do not currently ask about AD-related genetics or biomarkers. With regard to AD, elevated levels of Aβ are measurable years before clinical symptoms. Thus, adults still in the workforce could learn the results of biomarker tests, opening up the possibility for discrimination. Researchers must keep this in mind when designing disclosure protocols. While the safety and long-term effects of biomarker disclosure are still being determined, one option may be to recruit only retired adults into studies to mitigate potential workplace discrimination. Long term, however, it will be important for studies to recruit individuals still in the workforce given the focus on early intervention and temporal gap between Aβ accumulation and dementia symptoms. Strategies to mitigate discrimination

TABLE 1 Review of prior literature regarding Aβ disclosure in cognitively unimpaired people

Publication	Manuscript title	Sample	Study and location	Study design	Data collection protocol	Study findings
Impact of Conducting Disclosure						
[a]Grill et al. (2020)	Short-term psychological outcomes of disclosing amyloid imaging results to research participants who do not have cognitive impairment	1705 unimpaired (1167 with elevated Aβ, 538 with not elevated Aβ)	A4 Clinical Trial and LEARN prospective cohort, Multiple sites	Prospective cohort study	Psychological assessment was completed pre and post-disclosure (visit 1 and 6, respectively). The Concern About AD assessment was collected pre-disclosure (visit 1) and within 72 hours of disclosure (visit 3).	There were no statistically significant differences between participants with and without elevated Aβ in short-term increases of depression, anxiety, or suicidality. Compared to participants with not-elevated Aβ, participants with elevated Aβ reported increased concern about AD.
[a]Largent et al. (2020)	Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results	80 unimpaired	A4 Clinical Trial and LEARN prospective cohort (SOKRATES), University of Pennsylvania, USA	Prospective cohort study	Post-disclosure interviews 4–12 weeks and 1 year after disclosure	Participants with elevated Aβ contemplated making more health changes than not-elevated participants. Not-elevated Aβ participants reported relief
Wake et al. (2020)	disclosure of amyloid status for risk of alzheimer disease to cognitively normal research participants with subjective cognitive decline: a longitudinal study	42 unimpaired with subjective cognitive decline (10 Aβ-positive, 32 Aβ-negative)	Keio University, Japan	Participants recruited from memory clinic	Baseline and 6, 24, and 52 weeks after disclosure.	No significant differences in anxiety or depression between groups. Aβ-negative participants had significantly higher test-related distress at 52 weeks than Aβ-positive participants
Largent et al. (2019)	Attitudes toward physician-assisted death from individuals who learn they have an alzheimer disease biomarker	77 unimpaired	A4 Clinical Trial and LEARN prospective cohort (SOKRATES), University of Pennsylvania, USA	Prospective cohort study	Semi-structured interview 4-12 weeks after disclosure, follow-up interview at 12 months	Approximately 1 in 5 interviewees with elevated Aβ stated they would pursue physician assisted death (PAD) if they became cognitively impaired, were suffering, or were burdening others. These interviewees were relatively more likely to report preparing for the future (e.g., financial and legal planning). Baseline attitudes toward PAD do not change after learning Aβ result

(Continues)

TABLE 1 (Continued)

Publication	Manuscript title	Sample	Study and location	Study design	Data collection protocol	Study findings
Mattos et al. (2019)	Research use of ecological momentary assessment for adverse event monitoring following amyloid-β results	24 participants with MCI (12, amyloid positive, 12 amyloid negative)	University of Pittsburgh ADRC, USA	Prospective cohort study	Random phone calls and adverse event monitoring using EMA over 14 days after disclosure	EMA and standard adverse event monitoring can maximize early detection of negative psychological reactions to disclosure in participants with MCI
[a]Grill et al. (2018)	Reactions to learning a "not elevated" amyloid PET result in a preclinical Alzheimer's disease trial	33 unimpaired	A4 Clinical Trial, University of California Irvine, USA	Prospective cohort study	Disclosure and post-disclosure interviews Range of time between PET disclosure and interview was 3–30 months	Most participants without elevated amyloid stated they would adopt lifestyle changes if they had received an elevated result
[a]Wake et al. (2018)	The psychological impact of disclosing amyloid status to Japanese elderly: a preliminary study on asymptomatic patients with subjective cognitive decline	42 unimpaired with or without subjective cognitive decline	Keio University, Japan	Participants recruited from memory clinic	Before and after disclosure	State anxiety and depression did not change over time and were not different between elevated and non-elevated groups.
[a]Burns et al. (2017)	Safety of disclosing amyloid status in cognitively normal older adults	97 unimpaired	APEX exercise study, University of Kansas Alzheimer's Disease Center, USA	Prospective cohort study	Before and at disclosure, 6 weeks and 6 months post-disclosure	Low risk of psychological harm upon disclosure of Aβ results to cognitively unimpaired participants
[a]Lim et al. (2016)	Disclosure of positron emission tomography amyloid imaging results: A preliminary study of safety and tolerability	11 unimpaired	Australian Imaging, Biomarkers and Lifestyle study	Prospective cohort study	Baseline, 9 and 18 months follow-up	Disclosure of Aβ imaging did not have significant emotional or mood impacts. Those with elevated Aβ were more likely to make positive lifestyle changes
Participant and researcher attitudes toward disclosure						
[a]Vanderschaeghe et al. (2019)	Stakeholders' views on early diagnosis for Alzheimer's disease, clinical trial participation and amyloid PET disclosure: A focus group study	5 focus groups: informal caregivers (9), researchers (8), healthy elderly (10), nursing staff (6), clinicians (7))	Katholieke Universiteit Leuven, Belgium	Focus group study	Hypothetical scenarios were presented. Interviews on the focus groups responses were recorded and analyzed	Informal caregivers and researches wanted to know their Aβ PET scan result, healthy elderly, nursing staff and clinicians did not

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TABLE 1 (Continued)

Publication	Manuscript title	Sample	Study and location	Study design	Data collection protocol	Study findings
Armstrong et al. (2019)	Patient stakeholder versus physician preferences regarding amyloid PET testing	221 (107 patient stakeholders, 114 clinicians)	University of Maryland, USA	Focus group study	Surveyed patients, family members, dementia advocates, and clinicians on prospective population, outcomes, and harms of disclosure	Patients and caregivers valued having a dementia diagnosis, testing, and outcomes for asymptomatic populations more than clinicians
Grill et al. (2016)	Disclosure of amyloid status is not a barrier to recruitment in preclinical Alzheimer's disease clinical trials	132 self-reportedly unimpaired	ADRC, University of California Los Angeles, USA	Hypothetical clinical AD study with two conditions (with and without condition of learning amyloid PET results)	Likelihood of enrollment in the study	No difference between groups in willingness to participate indicating that requirement of biomarker disclosure may not pose a problem for recruitment to preclinical AD trials
[a]Ott et al. (2016)	A survey of knowledge and views concerning genetic and amyloid PET status disclosure	164 "cognitively intact"	Rhode Island Alzheimer Prevention Registry (RIPR), USA	Survey	25-item survey to characterize participant interest in disclosure	80% of participants reported wanting to learn their *APOE* and amyloid PET results.
[a]Gooblar et al. (2015)	Attitudes of research participants and the general public regarding disclosure of Alzheimer disease research results	219 unimpaired	KADRC, Washington University, USA	Randomized control survey (two conditions: education session with and without disclosure specific information)	Pre and post-education session	Interest in disclosure increases for participants with AD experience. Limitations with result interpretation may decrease interest in disclosure
[a]Shulman et al. (2013)	Using AD biomarker research results for clinical care: a survey of ADNI investigators	159 ADNI investigators and personnel	ADNI, University of Pennsylvania, USA	Survey	Anonymous online survey on: practices about returning results, attitudes about returning Aβ imaging results, explanations for attitudes, etc.	73% of ADNI researchers support disclosure to participants with MCI; 58% of ADNI researchers support disclosure to participants with normal cognition

(Continues)

TABLE 1 (Continued)

Publication	Manuscript title	Sample	Study and location	Study design	Data collection protocol	Study findings
Understanding disclosure results						
[a]Mozersky et al. (2018)	Comprehension of an elevated amyloid positron emission tomography biomarker result by cognitively normal older adults	50 unimpaired	A4 Clinical Trial (SOKRATES), University of Pennsylvania	Prospective cohort study	Post-disclosure interviews 4–12 weeks and 1 year after disclosure	Clinicians need to be prepared how to disclose the result of elevated Aβ to cognitively unimpaired individuals. Many want to know their risk for developing AD and how elevated their Aβ is
Ethical analysis and disclosure procedure development						
Taswell et al. (2019)	Avoiding methodological bias in studies of amyloid imaging results disclosure	N.A.	University of California San Diego, USA	Letter written in response to Grill et al. 2018	Analyzing studies by Grill et al., Wake et al., and Taswell et al.	Methodological bias can be avoided with multiple examiners/examination tools, multiple comparison groups, including observable life events as outcome measures, and larger sample sizes. There is no evidence of disclosure harming those without neuropsychiatric illness
Grill et al. (2019)	Response to "Avoiding methodological bias in studies of amyloid imaging results disclosure"	N.A.	University of California Irvine, USA	Letter written in response to Taswell et al. 2019	Analyzing Taswell et al. (2019)	Multiple methods and studies are necessary to increase confidence of social science research
[a]Vanderschaeghe et al. (2018)	From information to follow-up: Ethical recommendations to facilitate the disclosure of amyloid PET scan results in a research setting	4 studies on amyloid PET disclosure	Katholieke Universiteit Leuven, Belgium	Informal literature review	Empirical evidence from Aβ PET disclosure studies to guide facilitation of Aβ PET disclosure	Developed the six-step IDT-CRP method for amyloid PET disclosure. It includes informing the participant on risks and their rights, allowing the participant to make an informed decision about involvement, testing, ensuring the participant still wants to know result, returning the result, and following-up with the participant over a period of time.

(Continues)

TABLE 1 (Continued)

Publication	Manuscript title	Sample	Study and location	Study design	Data collection protocol	Study findings
Rabinovici et al. (2016)	Testing and disclosures related to amyloid imaging and Alzheimer's disease: Common questions and fact sheet summary	N.A.	Alzheimer's Association and NIA, USA	N.A.	Summary of information to date on Aβ with regards to its role in AD, imaging, and disclosure	This NIA-AA information sheet does not address disclosure of amyloid PET to cognitively unimpaired research participants, but states "… it is premature to use amyloid imaging to determine whether healthy people who do not have cognitive impairment could be at risk for AD"
Molinuevo et al. (2016)	Ethical challenges in preclinical Alzheimer's disease observational studies and trials: Results of the Barcelona summit	N.A.	Barcelona, Spain	Ethical analysis	Analysis of justifications for preclinical AD studies	Developing an accurate risk-benefit ratio for risk marker status disclosure (including Aβ PET) is a challenge incorporating a variety of considerations including public perception of AD
[a]Harkins et al. (2015)	Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants	Experts in informed consent for genetic testing or human Aβ imaging	University of Pennsylvania, USA	Best practices consensus development	Three rounds of modified Delphi Method	A4 study participants should receive verbal and written information about AD and Aβ imaging. Screening for anxiety and depression is necessary. Disclosure should be in person. Follow-up to assess impact of disclosure, depression, anxiety, and distress
Leuzy et al. (2014)	Use of amyloid PET across the spectrum of Alzheimer's disease: clinical utility and associated ethical issues	N.A.	McGill University, Canada	N.A.	Discussion of the development and use of amyloid PET.	Clinical utility of Aβ PET should be better established before widely disclosing Aβ PET results. Further, assessments of the cost-effectiveness of Aβ PET are needed
Roberts et al. (2013)	Amyloid imaging, risk disclosure and Alzheimer's disease: ethical and practical issues	N.A.	University of Michigan, USA	Ethical analysis	Discussion of key issues in disclosure of Aβ PET to asymptomatic individuals	There are many areas in the field of preclinical PET Aβ disclosure that require investigation, including the development of evidence-based education and counseling of participants

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TABLE 1 (Continued)

Publication	Manuscript title	Sample	Study and location	Study design	Data collection protocol	Study findings
Grill et al. (2013)	Should we disclose amyloid imaging result to cognitively normal individuals?	N.A.	University of California Los Angeles, USA	N.A.	Overview of clinical significance of Aβ, and pros and cons of disclosure	Clinical use of Aβ PET for unimpaired individuals is not yet justified. Studies suggest that disclosure of Aβ PET will have minimal psychological harm
Porteri et al. (2010)	Diagnosis disclosure of prodromal Alzheimer disease-ethical analysis of two cases	2 with memory symptoms	IRCCS Centro San Giovanni di Dio Fatebenefratelli, Italy	Case study	Ethical analysis of disclosure in two cases.	Disclosure was context specific and personalized to the patient
Systematic and literature Reviews						
Kim et al. (2019)	Disclosure of amyloid PET scan results: A systematic review	304 (233 cognitively unimpaired, 38 amnestic MCI, 33 patients/caregivers)	University of Pittsburgh ADRC, USA	Systematic literature review	N.A.	Seven studies were included in the analysis. The three studies collecting measures of depression or anxiety found no significant differences from baseline to follow-up or between Aβ-positive and Aβ-negative participants
[a]de Wilde et al. (2018)	Disclosure of amyloid positron emission tomography results to individuals without dementia: a systematic review	507 unimpaired	ABIDE, Vrije Universiteit Amsterdam, Netherlands	Systematic literature review	N.A.	Disclosure of Aβ PET result is not harmful regarding anxiety or uncertainty
Hughes et al. (2017)	Consent for the diagnosis of preclinical dementia states: A review	N.A.	University of Bristol, England	"Scoping" review	Performed literature review. Identified themes across the 10 papers from the literature review.	Four themes were identified in the 10 papers on issues around preclinical dementia disclosure: stigma, ethical issues, psychological burden, and language/

[a]Denotes that the study was cited in the Erickson et al. manuscript. Due to restrictions on the number of references allowed, not all of the studies on asymptomatic disclosure from the literature review were expressly discussed and cited. We have included them in this table for transparency in our literature review methods and reader convenience.

Abbreviations: Aβ, amyloid beta; AA, Alzheimer's Association; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; EMA, Ecological momentary assessment; IDT-CRP, information, decision, testing, confirmation, return of result, and postguidance; MCI, mild cognitive impairment; NIA, National Institute on Aging; PET, positron emission tomography.

TABLE 2 Summary of current practices in Aβ disclosure studies

Consideration	Specific practice
Ensure participant understanding of study	• Provide an education session on the biomarker (role in AD, limitations of testing, meaning of test results, potential outcomes of receiving this information) • Explain study procedures (PET scan, follow-up visits/calls) • Include assessment of participant understanding of study results in inclusion criteria
Effectively communicate result to participants	• Disclosure conducted by professional with experience interacting with participants • Use standardized language • Provide images when possible • Have participant say what their result means after disclosing to ensure understanding • Encourage asking questions multiple times throughout visits
Focus on participant safety	• Screen participants for significant anxiety, depression, and suicidality before enrolling • Continued follow up throughout study to assess psychosocial changes • Develop safety plan if participant needs more support following disclosure

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; PET, positron emission tomography.

therefore may include adequately informing participants of the risk of employment discrimination. An example of protections for individuals with knowledge of their disease risk can be found in the United States with the Genetic Information Nondiscrimination Act (GINA). GINA protects individuals with knowledge of their genetic risks from discrimination in the workplace and health-care insurance. Future policy initiatives, both in the United States and elsewhere, can use GINA as a template to protect individuals with disease-related biomarkers from discrimination in health care, the workplace, and beyond. Modifications to a GINA-like policy may include protections from life and disability insurance discrimination, as well as more broadly defining disease-related biomarkers to include different biomarker collection modalities (e.g., PET scans, blood tests, genetic tests, etc.).

5 | TRANSLATING AD BIOMARKER DISCLOSURE FROM RESEARCH TO CLINICAL SETTINGS—USE IN DIAGNOSIS AND MANAGEMENT OF COGNITIVE IMPAIRMENT

While Aβ PET scans are not currently a standard part of memory care, a U.S.-wide study, the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study, is assessing the current clinical utility of Aβ PET in Medicare beneficiaries who are cognitively impaired. Results from IDEAS suggest that use of Aβ PET scans may be associated with changes in clinical management for patients with cognitive impairment.[32] Similar results were also reported in a non-U.S. sample through the Alzheimer's Biomarkers in Daily Practice (ABIDE) project.[33] As a result, there may be more widespread use of Aβ PET scans for patients with cognitive impairment. A 2013 report on "Appropriate Use Criteria for Amyloid PET" was written by the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. The report asserts that disclosing Aβ PET results is only appropriate for individuals with cognitive impairment and that the prognostic value, or clinical validity, of Aβ PET positivity in cognitively unimpaired individuals requires further investigation. However, given the advancements since 2013 in our understanding of the preclinical pathological progression of AD and relevance of brain Aβ, Aβ PET (and potentially future blood-based AD biomarkers) may also have clinical utility for at-risk adults as the first potentially effective anti-Aβ therapy moves forward for U.S. Food and Drug Administration approval.[34] As such, evidence-based practices for safe and effective disclosure will be important for dissemination to clinical practice.

In addition to medication trials, non-pharmacological interventions may improve health and increase resilience to cognitive decline. A 2-year randomized control trial in Finland (FINGER) found that a multidomain lifestyle intervention could improve or maintain cognitive functioning in at-risk late-age people.[35] While there are mixed findings on the relationship of modifiable factors and Aβ on cognition, some studies suggest that worse health in combination with Aβ is related to poorer cognitive trajectories.[36,37] Regardless of the relationship between modifiable factors and AD pathophysiology, lifestyle plays a role in healthy aging and may be leveraged to improve aging trajectories in older adults. In 2019, the World Health Organization published guidelines for reducing risk of cognitive decline and dementia that included targeting lifestyle factors such as increasing physical activity, tobacco cessation, and management of comorbidities like hypertension and diabetes.[38] Although addressing modifiable risk factors may not directly reduce Aβ accumulation, reducing modifiable risk factors may slow or delay the onset of AD-related cognitive decline. Leveraging Aβ results and disclosing them as a risk factor for AD dementia may empower individuals to initiate activities to reduce modifiable risk factors, which in turn may result in improved health and/or reduced risk for cognitive decline.

6 | TRANSLATING AD BIOMARKER DISCLOSURE FROM RESEARCH TO CLINICAL SETTINGS—USE IN PREDICTING RISK AND PROGNOSIS FOR INDIVIDUAL PATIENTS

Clinical validity is described as "the predictive value of the biomarker, or the extent to which the biomarker distinguishes between those who will develop the disease and those who will not."[22] That is, in a clinical setting, a biomarker must provide information to clinicians about the presence of disease or eventual disease progression to be clinically valid. Common PET tracers used to determine presence of Aβ, such as [C-11] Pittsburgh Compound B (PiB), florbetapen, florbetapir, and

flutemetamol, bind selectively and specifically to the protein and have been validated in vivo and in *post mortem* human tissue.[39–41] In effect, we can be confident that the result of the Aβ PET scan is accurate.

There is more difficulty, however, in using that test result to predict individual risk for developing AD dementia. Ample evidence indicates that markers of elevated Aβ are associated with cognitive decline.[4,36,42] The pre-symptomatic phase of Aβ accumulation occurs over many years and perhaps decades. Because Aβ tracers were developed in the 2000s, there has not been sufficient time to fully characterize the prodromal stage of Aβ accumulation. Therefore, the proportion of adults with elevated Aβ biomarkers that will not go on to develop dementia symptoms remains unknown. Other factors may also impact prognosis including neurofibrillary tangle pathology, other brain pathology or dementia risk factors (e.g., vascular risk factors or cerebrovascular disease), time since elevated Aβ accumulation, and individual characteristics about the person (e.g., age and sociodemographic factors). Additionally, individuals with non-elevated Aβ PET scan results are at lower risk for cognitive decline than those with an elevated result; however, they may still develop Aβ pathology or cognitive decline in the future.

Despite presence of elevated Aβ not guaranteeing dementia development, large studies suggest that Aβ PET scan results are useful in predicting increased risk of AD dementia. For example, a population-based sample of more than 1500 people reported that the overall risk of developing clinical symptoms of dementia is elevated 2.6-fold in Aβ-positive versus Aβ-negative cognitively healthy participants.[43] Lifetime risks of dementia associated with elevated Aβ in adults aged 65 to 85 years have been calculated to be 13.8% to 29.3%, compared to lifetime risk estimates of 7.1% to 18.7% in similarly aged adults with non-elevated Aβ markers.[44] As we continue to discern the role of Aβ in AD dementia onset, we may better calculate risk estimates at the population and individual level.

7 | TRANSLATING AD BIOMARKER DISCLOSURE FROM RESEARCH TO CLINICAL SETTINGS—WHAT DO WE STILL NEED TO KNOW?

It is important to note that much of the available information about Aβ PET imaging is from cohort studies, which are not representative of the general population in terms of level of risk for AD and related dementias; race and ethnicity; sex; and other factors, such as education and socioeconomic status. When data from cohort studies are applied to the general population, it is likely that risk estimates will be overstated. Although the above risk predictions were developed from population-based studies, these studies were based on populations of primarily White adults. More inclusive studies are needed to characterize risk across education ranges, socioeconomic statuses, and in racial and ethnic groups that are under-represented in research. These additional data are needed to confirm if risk predictions are similar across populations. Evidence from population-based samples suggest that Black participants have higher rates of dementia and are more likely to exhibit dementia due to mixed pathology (e.g., AD and vascular disease) compared to White participants.[45] Although in vivo biomarker studies based on cohort studies suggest that Aβ PET scan and cerebrospinal fluid (CSF) results are similar across White and Black participants, group differences in CSF markers of neurofibrillary tangles (eg, p-tau) have been reported.[46,47] Pathophysiological progression in non-White samples needs to be further explored to determine whether different risk predictions would be expected in these populations.

Study cohorts also are skewed with more female participants, which may further confound generalizability. Prevalence for AD dementia is higher among females; however, this is in part driven by the longer life expectancies of females over males. Researchers are currently exploring the role of sex and gender in AD, including potential differences in disease mechanisms, pathways, and risk factors. There is still much to be learned about sex and gender differences in AD and advancements in this area may aid in better detection methods or treatments. For a more comprehensive discussion on sex and gender research in AD, refer to Mielke.[48]

Although current studies focus on Aβ PET disclosure, other methods of Aβ or tau measurement currently available or in development are also relevant to the current discussion. Aβ results from CSF and newer blood-based biomarkers may be disclosed. The amount of time an individual has had elevated Aβ may be more predictive of future cognitive decline and clinical outcomes. With the development of methods to quantify the duration of elevated brain Aβ, this information may be provided to individuals as opposed to a binary result (elevated or non-elevated). Tau, the other pathologic hallmark of AD, is more temporally related to dementia onset.[49,50] As validation of CSF and PET measures of tau continue, future studies may disclose tau status individually or in conjunction with Aβ status.

8 | RECOMMENDATIONS FOR NEXT STEPS

Table 3 provides a non-exhaustive list of potential future directions of AD biomarker disclosure studies based on gaps in the literature. The outlined ideas cannot be accomplished in one study and may prove to be cost-prohibitive. Identifying areas of critical need, while balancing study costs, is important for determining logical next steps. A relatively simple and low-cost next step can focus on the impact of disclosure on relationships between researchers and participants. Quantifying study retention, trust in medical research, and satisfaction with study experience can provide evidence for improved transparency and strengthen the argument for disclosing AD biomarkers.

Next, we recommend that best practices be established in the field for AD biomarker disclosure. While the studies published to date include recommendations for the development of disclosure protocols, there has yet to be consensus on best practices incorporating the findings from different studies. Best practices should include developing educational materials for a diverse audience (different educational backgrounds, cultural competencies, etc.), establishing a replicable protocol for conducting disclosure (e.g., in-person vs virtual, conducted by a clinician vs. study coordinator), and diversifying samples

TABLE 3 Future directions in Alzheimer's disease biomarker disclosure research

Key area	Research needed
Personal utility	• Increased engagement in activities that may reduce modifiable risk factors • Increased engagement in long-term care planning activities
Longer term psychosocial impacts	• Stigma • Subjective cognitive decline
Disclosure process	• Ensuring and improving understanding of biomarker result • Determining duration and type of follow-up support • Studying effectiveness of disclosure protocols in population-based or clinical samples
Trust in medical research	• Increased enrollment in ancillary studies or clinical trials • Increased retention in longitudinal cohort studies • Increased representation of participants from under-represented groups

Disclosing biomarkers other than binary Aβ PET result	• Duration of Aβ positivity
	• Blood-based markers of Aβ
	• Tau
	  ○ CSF markers
	  ○ PET markers
	  ○ Blood-based markers

Abbreviations: Aβ, amyloid beta; CSF, cerebrospinal fluid; PET, positron emission tomography.

for representative inclusion (e.g., socioeconomic status, race, education, family history).

9 | CONCLUSION: TO DISCLOSE OR NOT TO DISCLOSE?

While there are valid concerns regarding AD biomarker disclosure to cognitively unimpaired adults, additional research on the predictive value of biomarkers, interdisciplinary collaboration, and careful development of protocols and participant materials can strengthen the argument in favor of disclosure. Disclosing biomarker test results to research participants may promote autonomy and empower people to make healthy lifestyle changes and plan for their future. As we learn more about the role of AD biomarkers in disease progression, it is likely more studies will begin sharing biomarker test results with participants. Thus, it is critical that we develop best practices for disclosure and characterize the long-term effects of having knowledge of biomarker status. Doing so will promote safe, effective processes that include adequate follow-up to support participants. Furthermore, because researchers have a responsibility to uphold bi-directional communication and transparency,[24] disclosure may be one avenue to fulfill this duty while also bolstering the relationship between researchers and the communities/people who volunteer their data.

Indeed, disclosing AD-relevant biomarkers causes ripple effects outside of scientific research and into the policy realm. Currently, Aβ scans in cognitively unimpaired adults are mostly conducted in research settings. With earlier characterization of AD brain changes, development of novel blood-based biomarkers, and greater understanding of the meaning of brain changes in the context of AD risk, it is possible that biomarker scans or other tests may be conducted in a health care or DTC setting on cognitively healthy or "worried well" adults. While doing so may improve care or help individuals plan for their future, it may also lead to discrimination in the workplace and for different forms of insurance. It is paramount that as discussions on disease-relevant biomarker disclosure continue, advocacy for protections of individual biomarker knowledge occur too. The Genetic Information Nondiscrimination Act can serve as an example of designing policies that protect individuals with personal knowledge of disease-related biomarkers from workplace and health-care insurance discrimination. The future of AD biomarker disclosure is teeming with potential for exciting opportunities that intersect with public health, science communication, policy, and many other fields. Although more research is critically needed, current evidence suggests that the risks of disclosure do not clearly outweigh the benefits. Moving forward, responsible disclosure must continue to be conducted with an interdisciplinary approach that includes the perspectives of stakeholders, including research participants, researchers, health-care providers, and policy makers.

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CONFLICTS OF INTEREST

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