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A pragmatic, investigator-driven process for disclosure of amyloid PET scan results to ADNI-4 research participants

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Abstract

BACKGROUND: Prior studies of Alzheimer's disease (AD) biomarker disclosure have answered important questions about individuals' safety after learning and comprehending their amyloid PET results; however, these studies have typically employed highly structured disclosure protocols and focused on the psychological impact of disclosure (e.g., anxiety, depression, and suicidality) in homogeneous populations. More work is needed to develop flexible disclosure protocols and study outcomes in ethnoculturally representative samples.

METHODS: The Alzheimer's Disease Neuroimaging Initiative (ADNI) is formally incorporating amyloid PET disclosure into the newest protocol (ADNI-4). Participants across the cognitive spectrum who wish to know their amyloid PET results may learn them. The pragmatic disclosure

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process spans four timepoints: (1) a pre-disclosure visit, (2) the PET scan and its read, (3) a disclosure visit, and (4) a post-disclosure check-in. This process applies to all participants, with slight modifications to account for their cognitive status. In designing this process, special emphasis was placed on utilizing investigator discretion. Participant measures include perceived risk of dementia, purpose in life, and disclosure satisfaction. Investigator assessment of the disclosure visit (e.g., challenges encountered, topics discussed, etc.) is also included.

RESULTS: Data collection is ongoing. Results will allow for more robust characterization of the impact of learning amyloid PET results on individuals and describe the perspectives of investigators.

CONCLUSION: The pragmatic design of the disclosure process in ADNI-4 coupled with the novel participant and investigator data will inform future disclosure practices. This is especially important as disclosure of biomarker results expands in research and care.

Keywords

Alzheimer's disease; Biomarker disclosure; Pragmatic

1. Introduction

In recent years, the Alzheimer's disease (AD) field has moved towards a biological definition of disease[1]. Biological markers, or biomarkers, of the pathological processes defining AD—including deposition of beta-amyloid fibrillar plaques and accumulation of hyperphosphorylated tau-based neurofibrillary tangles[2]—are detectable years before the onset of clinical symptoms and continue to accumulate as the disease progresses[1]. These biomarkers can be detected *in vivo* in asymptomatic and symptomatic individuals using modalities such as positron emission tomography (PET) imaging or cerebrospinal fluid (CSF) assays. Biomarker testing can serve various purposes in AD research including characterizing disease progression across the disease continuum. In clinical trials, the presence of one or more AD biomarkers is often an eligibility criterion—for example, because the biomarker enables characterization of the patient population (e.g., stage/severity of disease) or confirms the presence of a drug target[3]. In observational studies, such as the Alzheimer's Disease Neuroimaging Initiative[4–6] (ADNI; NCT05617014)—a longitudinal study aimed at validating biomarkers for AD clinical trials—biomarker testing informs understanding of the natural history of the disease[7]. Beta-amyloid has, to date, been the predominant biomarker in AD: amyloid accumulation is among the first AD-related changes in the brain[8] and is associated with increased risk of cognitive decline[9–12], including progression to Mild Cognitive Impairment (MCI) and dementia[13–16].

Inclusion of biomarker testing in AD research naturally fueled both interest in the disclosure of test results and debates about the appropriateness of such disclosure[7]. Because the presence of beta-amyloid was an eligibility requirement for these trials, disclosure was thought to promote trial feasibility and respect for persons. As such, clinical trials of anti-amyloid therapies led the way in disclosing results[17]. Using genetic disclosure—especially of *APOE*[18,19], a gene associated with late-onset AD—as a model, researchers developed rigorous disclosure protocols that emphasized participant education

and safety[7,17]. Implementation of these disclosure protocols in clinical trials made it possible to systematically study the effects of disclosure.

The results from these initial disclosure studies provided evidence that AD biomarker information could be delivered effectively and safely. With pre-test education and counseling, individuals generally understand the meaning and import of their beta-amyloid results, which to date have been returned as a categorical result (e.g., “elevated” vs. “not elevated” or “positive” vs. “negative”). Moreover, disclosure is safe; learning one’s beta-amyloid result does not result in symptoms of anxiety or depression, nor does it result in suicidality[7,20–24]. Nevertheless, individuals do have an emotional reaction to disclosure[25–28]. For *cognitively unimpaired* participants, post-disclosure distress—measured using the Impact of Events Scale (IES)—varies with the result; individuals who learn an “elevated” result report more distress than those who learn a “not elevated” result[23,25,29,30]. Similarly, some *cognitively impaired* individuals experience emotional distress after learning they have “elevated” beta-amyloid, as reflected in increased IES scores[31]. Notably, increases in post-disclosure distress have been minimal (i.e., not crossing clinical thresholds) and temporary. Those learning a “not elevated” beta-amyloid result have experienced a range of reactions. Whereas some persons with MCI who receive a “not elevated” result experience relief (given the reduced likelihood of symptom progression and that AD is unlikely the cause of current symptoms), others express frustration because they lack an explanation for their impairment[7]. Studies of disclosure have also demonstrated the value of AD biomarker results to individuals. Although results may not be *medically* actionable in many cases, they are *personally* actionable. They influence individuals’ health behaviors and an array of life plans, from updating a will or advance directive to making decisions about when to retire or where to live[28,32–34]. A notable limitation of these disclosure studies is that, like the clinical trials they were incorporated into, their participants have been largely made up of non-Latino/a/x White, college-educated participants.

There has been a shift from reticence to readiness to disclose AD biomarkers in the research community[35], though it remains unclear how clinicians will incorporate AD biomarker disclosure into their practice. This shift reflects the mounting evidence that disclosure can be performed safely for both cognitively unimpaired and impaired populations. Further, research participants have clearly expressed that they want to know their results[36]. Because participants value these results, disclosure may help with recruitment and retention. Additionally, with U.S. Food and Drug Administration (FDA) approval of new drugs, there is recognition that biomarker results hold clinical value for some individuals. As a sign of the reticence-to-readiness shift, the National Institute on Aging (NIA) recently called on NIA-funded Alzheimer’s Disease Research Centers (ADRCs), which have historically had varied approaches to disclosure[37], to “assure appropriate disclosure of biomarker and other results[38].” Guidance on biomarker disclosure was recently made available to ADRCs[39].

AD biomarker disclosure processes have generally been highly structured, reflecting the tightly controlled research settings in which disclosure was happening as well as the need to rigorously study a novel practice[7]. With AD biomarker testing now occurring on a larger scale and across more settings, it is time for the science of disclosure to evolve in two important ways. First, the goals in this new phase should include design and

implementation of flexible disclosure processes that rely more on clinical judgment than on prescriptive steps for how the encounter should unfold. Yet, while increasing flexibility, it is important to continue assessing effectiveness—that is, how well disclosure works in less-controlled environments to meet its chief goals of educating and empowering individuals and ensuring their safety. Second, there is an urgent need for evidence on disclosure with historically underrepresented populations (URPs), including those from minoritized ethnocultural backgrounds, low education, and low resource settings who are at increased risk for dementia and/or worse dementia care access and outcomes[40].

ADNI began in 2004, and after nearly two decades, is recognized as a preeminent AD biomarker study[5,41]. In 2022, ADNI leadership decided that, beginning in Summer 2023, investigators would disclose amyloid PET results to participants at the 56 ADNI-4 sites. This decision was driven by the priority placed in ADNI-4 on recruiting and retaining participants from historically underrepresented groups utilizing a culturally-informed, community-engaged research approach[42,43]. Incorporating disclosure into ADNI required devising a pragmatic disclosure framework that could easily be incorporated into existing ADNI workflows and was adaptable to the needs of a heterogenous group of investigators (e.g., different specialties) and participants (e.g., different levels of cognitive impairment, from communities historically underrepresented in research). The resulting pragmatic disclosure process is intended to foster investigator discretion and to minimize investigator and participant burden as well as to facilitate learning from investigator and participant experiences. Given the number of sites, investigators, and participants involved, this presented a unique opportunity to study the effects of disclosure in a more representative sample.

This article describes the process developed for ADNI amyloid PET disclosure, which may be informative for other studies developing AD biomarker disclosure protocols, as well as health systems preparing to disclose results. The paper describes the data we are collecting to deepen our understanding of disclosure. With about 20 years of data characterizing disease progression, ADNI has transformed the field's understanding of AD[4–6,41]. Investigating disclosure within ADNI will further expand the study's contributions to clinical trials and clinical practice as well as for patients, families, and policy makers.

2. Methods

2.1 Developing the disclosure framework

ADNI assembled a "disclosure team" with expertise in the design, implementation, and study of AD biomarker disclosure in longitudinal cohort studies and clinical trials (CME, JK, JDG, KH, EAL) to create an evidence-based, pragmatic amyloid disclosure framework that could easily be imbedded into the flow of ADNI-4 visits (See Figure 1). This framework addressed: which participants would be suitable for disclosure (§2.2); which ADNI-4 team members could disclose results (§2.3); the content and timing of the disclosure process (§2.4); and data collection (§2.5).

The disclosure team developed the disclosure framework and supporting materials in collaboration with ADNI leadership and key stakeholders, including leaders from the

Clinical Core, which oversees clinical activities and data management; the PET Core, which is focused on protocols for acquiring, processing, and analyzing the PET scans collected in ADNI; the Engagement Core, which is focused on health equity and improving enrollment and retention of ADNI participants, with a special focus on improving the representativeness of the ADNI cohort; and the Coordination Center. The Engagement Core then shared the first version of the disclosure framework and key supporting materials with ADNI-4 Community-Science Partnership Board (CSPB; which includes ADNI participants, community stakeholders, health equity experts, and ADNI scientists) during its quarterly meeting in April 2023 for their input and guidance on how these materials were viewed and could be improved for use with URPs.

2.1.i Incorporating community input into the disclosure framework—Overall, ADNI CSPB members strongly endorsed ADNI's efforts to create a systematic approach to disclose to PET results to all participants in receiving results. They also expressed concerns with the density and level of complexity of the materials for URP participants. The Engagement Core reported this feedback to the ADNI leadership. Based on this feedback, the participant facing materials were reviewed to adapt language to an 8th grade reading level while maintaining accuracy.

Looking forward, the disclosure team will solicit feedback from ADNI site investigators and participants, particularly those from URPs, who go through the disclosure process, as described below, as well as the CSPB for a review and feedback on updated materials. Their feedback will allow for iterative refinement of the disclosure framework and materials.

2.2 Participants

To be eligible for ADNI-4, participants must: be between the ages of 50 and 99; have a Geriatric Depression Scale (GDS) score less than 10; be literate and speak English or Spanish fluently; and have a study partner willing to accompany them to some visits or to provide information remotely. Individuals with any significant neurologic disease are excluded (for full list see https://clinicaltrials.gov/ct2/show/NCT05617014). Participants will be allowed to take disease-modifying drugs—including anti-amyloid therapies that result in a reduction in amyloid burden on imaging tests—and continue participating in ADNI.

Cognitively unimpaired and impaired (MCI or dementia) ADNI-4 participants who undergo an amyloid PET scan are eligible for disclosure subject to investigator assessment of appropriateness, discussed in §2.3.iii. Investigators will disclose amyloid PET scan results to eligible participants who consent to learning their results. Eligible participants will have the opportunity to learn the results from each of 2–3 amyloid PET scans they receive over the 5-year study period.

2.2.i. Sample Size—ADNI-4 will enroll around 1,500 participants: 40% cognitively unimpaired, 40% MCI, and 20% dementia[44]. Around 750 enrollees will rollover from ADNI-3 and 750 will be new enrollees. A goal of ADNI-4 is that 50–60% of new enrollees will be comprised of individuals from URPs. Given that biomarker disclosure studies have generally not enrolled representative samples, this is an important opportunity for ongoing

learning[7,45]: the participant data collected in ADNI-4 will more accurately reflect the aging population in the United States[46].

2.3 Disclosing Investigators

Disclosure will be performed by ADNI investigators who either (1) are clinically trained—for instance, as a physician, nurse practitioner, or (neuro)psychologist—and have experience in the diagnosis and care of persons with AD; or (2) have approval from the Alzheimer's Therapeutic Research Institute (ATRI). ATRI will take into account the individual's past experience interfacing with research participants and their expertise in AD research. In addition, disclosing investigators must have permission from their site PI. Regardless of prior experience disclosing amyloid PET scan results, ADNI leadership requires disclosing investigators to read through the training manual, described next, before disclosing results to ADNI-4 participants.

2.3.i. Investigator Training—The disclosure team developed a training manual that functions as a resource for disclosing investigators. It provides a review of what is known about AD biomarker disclosure, an overview of the disclosure process, and a table including frequently asked questions (FAQs) with responses. Relative risk estimates for conversion to MCI or dementia for participants based on cognitive status (unimpaired vs. MCI) and amyloid PET result (elevated vs. not elevated) are also included in the training manual (Figure 2). These estimates use ADNI cohort data and may help contextualize the amyloid PET result and risk of AD dementia during the disclosure visit. The manual provides examples of how an investigator might convey a point or communicate a result, though it is neither a formula nor a script. The training manual emphasizes the importance of investigator discretion.

Members of the disclosure team presented an overview of the disclosure process at the March 2023 ADNI investigator meeting; this presentation was recorded and is available to ADNI investigators.

2.4 The Disclosure Process

As summarized in Figure 1, the disclosure process spans four timepoints: (1) a pre-disclosure visit (occurring at the time of an ADNI in-clinic visit), (2) the scan and read (occurring as a part of an ADNI in-clinic visit), (3) a disclosure visit (a separate visit occurring after the ADNI in-clinic visit), and (4) a post-disclosure check-in (a separate visit occurring after the ADNI in-clinic visit and disclosure visits). This process applies to all participants, with slight modifications to account for their cognitive status. Because ADNI-4 participants undergo amyloid PET imaging every two years, they may go through the disclosure process more than once.

Materials developed for the disclosure process are available upon request from the authors.

2.4.i. Pre-Disclosure Education—Pre-disclosure education is incorporated into an existing in-clinic ADNI-4 visit. The goal is to educate participants about AD biomarkers, particularly beta-amyloid, and to prepare them to make an informed choice about whether to

learn their own amyloid PET scan result. During this visit, participants receive a participant education sheet that includes information at an 8th grade reading level on: AD; the role of beta-amyloid as a risk factor for cognitive decline; possible results of an amyloid PET scan (i.e., “elevated” vs. “not elevated”); and other considerations, such as test limitations and how learning results may affect interpersonal relationships or insurability. The education sheet also provides relative risk estimates for conversion to MCI or dementia, derived from ADNI cohort data, for participants based on cognitive status (unimpaired or MCI, respectively) and amyloid PET scan result (elevated vs. not elevated) (Figure 2). These materials were reviewed by CSPB and updates were made accordingly based on CSPB feedback.

2.4.ii. Amyloid PET Scan and Read—ADNI-4 participants undergo amyloid PET imaging using florbetapir (Amyvid), florbetaben (Neuraceq), or flutafuranol (NAV-4694) every two years. Scans are acquired and processed to account for scanner differences. Quantitative cortical standardized uptake volume ratio (SUVr) and centiloid (CL) measures are calculated according to standards established by ADNI’s PET Core[47,48], and tracer-specific quantitative positivity thresholds are applied[49]. The PET Core performs visual reads on all scans using criteria defined by the package insert for each tracer to determine if the scan is “elevated” or “not elevated.” If the mean cortical SUVr and the visual read of the scan are discordant, a final adjudication is rendered at a consensus conference. Results, including visual read, SUVr, regions of tracer binding, and scan images, are made available to ADNI investigators at the participant’s study site via ADNI’s secure study website, typically within 12 weeks of scan acquisition.

2.4.iii. Disclosure Visit—Disclosure visits are a new addition to the ADNI-4 protocol. They may be held in-person or via videoconference, depending on participant preference, and sites are encouraged to allot 45 to 60 minutes for the visit. This visit will typically occur around 12 weeks after the amyloid PET scan (pending availability of results and scheduling); this waiting period offers participants an important opportunity to reflect on whether they want to learn their result. The central goals of the disclosure visit are to: (1) ensure both that disclosure is appropriate for the participant and that they want to learn their result; and if yes to both, (2) disclose the result in a manner that facilitates participant understanding and appreciation.

Participants are asked to have their ADNI-4 study partner or another support person—typically a family member or friend—accompany them to the disclosure visit. This is a requirement for participants with an MCI or dementia diagnosis. In addition to reflecting research practice, the request to have a support person present is consistent with practice in clinical memory care, as patients are often asked to bring someone to visits who can aid in providing critical information for diagnosis and care planning. The decision to make the presence of a study partner or other support person at the disclosure visit optional, rather than obligatory, for cognitively unimpaired participants was based on evidence suggesting some participants, particularly those from URPs, may have greater difficulty arranging for a study partner to join them at visits[50,51].

The disclosure visit has three components, which mirror practices to disclose sensitive results in clinical care settings. To help facilitate the disclosure visit, we developed an optional visit organizer that provides disclosing investigators with an overview of the visit components as well as space to take notes.

First, as part of the pragmatic design of this process, disclosing investigators are expected to exercise clinical judgment to determine if disclosure is appropriate. At the investigator's discretion, validated measures of depression, anxiety, or suicidality may be administered during the disclosure visit to gain a deeper understanding of the participant's psychological state. The presence of psychiatric symptoms is not an absolute contraindication to disclosure, as psychiatric symptoms may be linked to changes in cognition[52]; however, such symptoms may inform a determination that disclosure would not be advisable at this time. If the investigator deems disclosure inappropriate, they will conclude the visit. If the investigator decides it is appropriate to proceed, they confirm the participant wants to learn their result. Participants may opt not to proceed with disclosure at any point during the visit.

Second, the investigator is encouraged to review the two possible amyloid PET scan results (i.e., "elevated" or "not elevated") and their meaning, taking into account whether the participant is cognitively unimpaired or impaired, before returning the participant's result. After sharing the result, the investigator may elect to share the participant's PET scan image or the quantitative information from the scan (e.g., tracer SUVr) to facilitate their explanation of the result or to aid the participant's understanding. As noted in §2.2, ADNI-4 participants will undergo multiple amyloid PET scans and will have the option to learn the results of each scan. Site investigators may choose to incorporate discussion of any prior amyloid PET scan results—for example, to describe change over time. Participants are allowed to be on anti-amyloid therapies while participating in ADNI-4; this raises the possibility that investigators might discuss how therapy has affected the amyloid PET scan (e.g., going from an "elevated" to "not elevated" result).

Finally, after returning the result, investigators are asked to ensure participant understanding and, if the participant is unsure of the result or its meaning, to walk through their result again. This is also an opportunity for participants to ask questions. At the conclusion of the visit: a) participants receive a written report that includes their result and a standardized summary of its meaning and b) investigators will complete a feedback survey as described in §2.5.ii.

2.4.iv. Post-Disclosure Check-In—Within a week of the disclosure visit, the site investigator or a research coordinator follows up with participants via telephone. The goal is to assess emotional distress, if any, in the wake of biomarker disclosure and to collect additional participant measures, as described in §2.5.i.

2.5. Data and Data Collection

2.5.i. Participant Data—Participant measures are summarized in Table 1. Participant measures were selected to build on existing knowledge of the impact of learning AD biomarker information.

During the pre-disclosure education session, participants will answer questions about their: previous knowledge of amyloid PET; anticipated amyloid PET scan result ("elevated" vs. "not elevated"); and confidence in that anticipated result (scale of 0–100%). Participants without dementia (unimpaired or MCI) will answer questions about their perceived risk of AD dementia, estimating their "chance" of developing dementia overall and relative to others their age. Participants will also complete the 14-item Ryff Psychological Well-Being[53,54] Purpose in Life subscale. Purpose in life is one aspect of psychological well-being and refers to the central motivating aims of a person's life and the meaning a person makes from their life experiences[55,56]. Returning amyloid PET results has been shown to have an emotional impact that is not captured by standard psychological measures of anxiety, depression, or suicidality. The Ryff is a novel inclusion and is expected to help characterize post-disclosure reactions[57]. Per existing ADNI protocol, participants will also complete the GDS[58,59] during this visit. Prior studies have shown that there are no significant changes from baseline in anxiety, depression, or suicidality following disclosure. Given the consistency of these results, the disclosure team determined these measures were not needed.

That said, during the disclosure visit, to aid in assessing the appropriateness of disclosure for a given participant, investigators may choose to administer the GDS, State Trait Anxiety Inventory, or Columbia-Suicide Severity Rating Scale. None of these items are, however, required. Outside of the administration of these questionnaires at the investigator's discretion, participants will not complete any additional questionnaires at the disclosure visit. See §2.5.ii for the investigator data collected at the disclosure visit.

During the post-disclosure check-in, one-week after the disclosure visit, the Impact of Events[60] (IES) Intrusion and Avoidance subscales will be administered to characterize participant distress. Prior studies using the IES have consistently shown small and temporary increases in post-disclosure distress. Because prior study populations have been predominantly White, college-educated participants, capturing post-disclosure distress within ADNI-4 offers the opportunity to see if such results generalize in a more representative sample. Participants will also be asked to recall their amyloid result and its meaning. Participants without dementia (unimpaired or MCI) will be asked again about their perceived risk of dementia to see if their valuation has changed in light of learning their amyloid PET result. To gather quality improvement information, participants will report on how useful learning their result was, whether they regret learning their result, and their satisfaction with the disclosure visit. Participants will also be asked with whom they shared their result with, as prior research has shown individuals engage in selective sharing[27].

At ongoing (bi)annual in-clinic ADNI visits, participants will answer the same questions related to recall of result, comprehension of result, perceived risk of dementia (unimpaired or MCI only), and value of learning their result. The Ryff[53] and IES[60] will also be administered annually. Participants will also be asked about any behavior changes they made because of the disclosure visit, including changes to future planning (e.g., updating a will) and lifestyle (e.g., exercising more). Per the ADNI protocol, the GDS[58,59] will be administered.

2.5.ii. Investigator Data—The experiences of individuals performing AD biomarker disclosure have largely been neglected in prior studies of disclosure. The inclusion of biomarker disclosure in ADNI-4 offers an opportunity to begin addressing this gap. At the conclusion of each disclosure visit, investigators will be asked to reflect on the visit. They will rate the participant's understanding of their amyloid PET scan result and emotional reaction to it; record topics discussed with the participant during the visit (e.g., other AD dementia risk factors, PET scan image, SUVr value, disease-modifying therapies, or how the present scan compared to any prior scans); note challenges they encountered; rate their confidence with different elements of the visit (e.g., answering participant questions); and provide an overall visit rating. Logistics of the visit will also be collected, including whether the result was disclosed (and if not, why not) and length of visit. These data will be used to characterize the investigator experience disclosing amyloid PET results within ADNI-4 and suggest ways to improve biomarker disclosure moving forward. Further, because anti-amyloid therapies are relatively new and have had limited uptake in clinical practice to date, this is a novel opportunity to understand how investigators discuss the effects of disease-modifying therapies.

2.6 Human Subjects Protections

The ADNI-4 protocol, including disclosure of amyloid PET scan results, was reviewed and approved by an Advarra institutional review board (IRB) (#Pro00064250). Consent for biomarker disclosure is included within the broader consent for ADNI-4. Learning amyloid PET results is optional and not required for participation in ADNI-4.

3. Conclusion

ADNI is one of the largest studies to date to incorporate AD biomarker disclosure and thus is an opportunity both to test a more flexible, pragmatic approach to disclosure that could be implemented in real-world settings, better inform disclosure policies and procedures with URPs, and also to deepen knowledge of the participant and investigator experience. The numbers of participants and disclosures per participant, participant diversity, and the variety of disclosing investigators across 56 sites mean that compared to prior studies of disclosure, ADNI-4 offers a closer approximation of real-world settings. In addition, disclosing to participants who are taking anti-amyloid therapies presents a novel opportunity to explore discussion of amyloid PET scans in the context of treatment.

The pragmatic disclosure process outlined here focuses on supporting investigator discretion through streamlined training and provision of resources while still promoting participant understanding and well-being. Studying the implementation of this flexible disclosure process will illuminate aspects that functioned well and those that merit revisiting. This information will usher in a new phase of the science of disclosure and is crucial to the implementation of disclosure processes in real-world settings with increasingly diverse patient populations.

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References

1. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535–562. doi:10.1016/j.jalz.2018.02.018 [PubMed: 29653606]
2. Perl DP. Neuropathology of Alzheimer's Disease. Mt Sinai J Med. 2010;77(1):32–42. doi:10.1002/msj.20157 [PubMed: 20101720]
3. Kim SYH, Karlawish J, Berkman BE. Ethics of genetic and biomarker test disclosures in neurodegenerative disease prevention trials. Neurology. 2015;84(14):1488–1494. doi:10.1212/WNL.0000000000001451 [PubMed: 25762713]
4. Weiner MW, Veitch DP, Aisen PS, et al. Impact of the Alzheimer's Disease Neuroimaging Initiative, 2004 to 2014. Alzheimers Dement. 2015;11(7):865–884. doi:10.1016/j.jalz.2015.04.005 [PubMed: 26194320]

5. Weiner MW, Veitch DP, Aisen PS, et al. Recent publications from the Alzheimer's Disease Neuroimaging Initiative: Reviewing progress toward improved AD clinical trials. Alzheimer's & Dementia. 2017;13(4). doi:10.1016/j.jalz.2016.11.007
6. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's Disease Neuroimaging Initiative 3: Continued innovation for clinical trial improvement. Alzheimers Dement. 2017;13(5):561–571. doi:10.1016/j.jalz.2016.10.006 [PubMed: 27931796]
7. Erickson CM, Chin NA, Johnson SC, Gleason CE, Clark LR. Disclosure of preclinical Alzheimer's disease biomarker results in research and clinical settings: Why, how, and what we still need to know. Alzheimers Dement (Amst). 2021;13(1):e12150. doi:10.1002/dad2.12150 [PubMed: 33665341]
8. Jack CR, Knopman DS, Jagust WJ, et al. Update on hypothetical model of Alzheimer's disease biomarkers. Lancet Neurol. 2013;12(2):207–216. doi:10.1016/S1474-4422(12)70291-0 [PubMed: 23332364]
9. Petersen RC, Wiste HJ, Weigand SD, et al. Association of Elevated Amyloid Levels With Cognition and Biomarkers in Cognitively Normal People From the Community. JAMA Neurol. 2016;73(1):85–92. doi:10.1001/jamaneurol.2015.3098 [PubMed: 26595683]
10. Mormino EC, Papp KV. Amyloid accumulation and cognitive decline in clinically normal older individuals: implications for aging and early Alzheimer's disease. J Alzheimers Dis. 2018;64(Suppl 1):S633–S646. doi:10.3233/JAD-179928 [PubMed: 29782318]
11. Sperling RA, Donohue MC, Raman R, et al. Association of Factors With Elevated Amyloid Burden in Clinically Normal Older Individuals. JAMA Neurol. 2020;77(6):735–745. doi:10.1001/jamaneurol.2020.0387 [PubMed: 32250387]
12. Koscik RL, Betthauser TJ, Jonaitis EM, et al. Amyloid duration is associated with preclinical cognitive decline and tau PET. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2020;12(1):e12007. doi:10.1002/dad2.12007
13. Ma Y, Zhang S, Li J, et al. Predictive accuracy of amyloid imaging for progression from mild cognitive impairment to Alzheimer disease with different lengths of follow-up: a meta-analysis. [Corrected]. Medicine (Baltimore). 2014;93(27):e150. doi:10.1097/MD.0000000000000150 [PubMed: 25501055]
14. Iaccarino L, Chiotis K, Alongi P, et al. A Cross-Validation of FDG- and Amyloid-PET Biomarkers in Mild Cognitive Impairment for the Risk Prediction to Dementia due to Alzheimer's Disease in a Clinical Setting. J Alzheimers Dis. 2017;59(2):603–614. doi:10.3233/JAD-170158 [PubMed: 28671117]
15. Rowe CC, Bourgeat P, Ellis KA, et al. Predicting Alzheimer disease with β-amyloid imaging: results from the Australian imaging, biomarkers, and lifestyle study of ageing. Ann Neurol. 2013;74(6):905–913. doi:10.1002/ana.24040 [PubMed: 24448836]
16. Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. Alzheimers Dement. 2018;14(8):981–988. doi:10.1016/j.jalz.2018.03.005 [PubMed: 29802030]
17. Harkins K, Sankar P, Sperling R, et al. Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants. Alzheimers Res Ther. 2015;7(1):26. doi:10.1186/s13195-015-0112-7 [PubMed: 25969699]
18. Roberts JS, Green RC. Disclosing ApoE genotype status to individuals at risk for Alzheimer's disease: Applying lessons learned from the reveal study to prevention treatment trials. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2015;11(7):P214. doi:10.1016/j.jalz.2015.07.230
19. Roberts JS, Patterson AK, Uhlmann WR. Genetic testing for neurodegenerative diseases: Ethical and health communication challenges. Neurobiol Dis. 2020;141:104871. doi:10.1016/j.nbd.2020.104871 [PubMed: 32302673]
20. Bemelmans SASA, Tromp K, Bunnik EM, et al. Psychological, behavioral and social effects of disclosing Alzheimer's disease biomarkers to research participants: a systematic review. Alzheimers Res Ther. 2016;8. doi:10.1186/s13195-016-0212-z

21. de Wilde A, van Buchem MM, Otten RHJ, et al. Disclosure of amyloid positron emission tomography results to individuals without dementia: a systematic review. Alzheimers Res Ther. 2018;10:72. doi:10.1186/s13195-018-0398-3 [PubMed: 30055660]
22. Grill JD, Raman R, Ernstrom K, et al. Short-term Psychological Outcomes of Disclosing Amyloid Imaging Results to Research Participants Who Do Not Have Cognitive Impairment. JAMA Neurology. 2020;77(12):1504–1513. doi:10.1001/jamaneurol.2020.2734 [PubMed: 32777010]
23. Caprioglio C, Ribaldi F, Visser LNC, et al. Analysis of Psychological Symptoms Following Disclosure of Amyloid–Positron Emission Tomography Imaging Results to Adults With Subjective Cognitive Decline. JAMA Network Open. 2023;6(1):e2250921. doi:10.1001/jamanetworkopen.2022.50921 [PubMed: 36637820]
24. Mozersky J, Sankar P, Harkins K, Hachey S, Karlawish J. Comprehension of an Elevated Amyloid Positron Emission Tomography Biomarker Result by Cognitively Normal Older Adults. JAMA Neurol. 2018;75(1):44–50. doi:10.1001/jamaneurol.2017.2954 [PubMed: 29059270]
25. Burns JM, Johnson DK, Liebmann EP, Bothwell RJ, Morris JK, Vidoni ED. Safety of disclosing amyloid status in cognitively normal older adults. Alzheimers Dement. 2017;13(9):1024–1030. doi:10.1016/j.jalz.2017.01.022 [PubMed: 28263740]
26. Grill JD, Cox CG, Kremen S, et al. Patient and caregiver reactions to clinical amyloid imaging. Alzheimers Dement. 2017;13(8):924–932. doi:10.1016/j.jalz.2017.01.001 [PubMed: 28174068]
27. Largent EA, Stites SD, Harkins K, Karlawish J. 'That would be dreadful': The ethical, legal, and social challenges of sharing your Alzheimer's disease biomarker and genetic testing results with others. Journal of Law and the Biosciences. 2021;8(1):lsab004. doi:10.1093/jlb/lsab004
28. Largent EA, Harkins K, van Dyck CH, Hachey S, Sankar P, Karlawish J. Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results. PLOS ONE. 2020;15(2):e0229137. doi:10.1371/journal.pone.0229137 [PubMed: 32053667]
29. Grill JD, Cox CG, Harkins K, Karlawish J. Reactions to learning a "not elevated" amyloid PET result in a preclinical Alzheimer's disease trial. Alzheimers Res Ther. 2018;10:125. doi:10.1186/s13195-018-0452-1 [PubMed: 30579361]
30. Wake T, Tabuchi H, Funaki K, et al. The psychological impact of disclosing amyloid status to Japanese elderly: a preliminary study on asymptomatic patients with subjective cognitive decline. Int Psychogeriatr. 2018;30(5):635–639. doi:10.1017/S1041610217002204 [PubMed: 29094656]
31. Lingler JH, Sereika SM, Butters MA, et al. A Randomized Controlled Trial (RCT) of Amyloid Positron Emission Tomography (PET) Results Disclosure in Mild Cognitive Impairment (MCI). Alzheimers Dement. 2020;16(9):1330–1337. doi:10.1002/alz.12129 [PubMed: 32588971]
32. Vanderschaeghe G, Vandenberghe R, Dierickx K. Stakeholders' Views on Early Diagnosis for Alzheimer's Disease, Clinical Trial Participation and Amyloid PET Disclosure: A Focus Group Study. Bioethical Inquiry. 2019;16(1):45–59. doi:10.1007/s11673-019-09901-9 [PubMed: 30868358]
33. Grill JD, Apostolova LG, Bullain S, et al. Communicating mild cognitive impairment diagnoses with and without amyloid imaging. Alzheimers Res Ther. 2017;9(1):35. doi:10.1186/s13195-017-0261-y [PubMed: 28472970]
34. Clark LR, Erickson CM, Jonaitis EM, et al. Anticipated reactions to learning Alzheimer's disease biomarker results. Alzheimer's Research & Therapy. 2022;14(1):85. doi:10.1186/s13195-022-01027-2
35. Grill JD, Karlawish J. Disclosing Alzheimer Disease Biomarker Results to Research Participants. JAMA Neurol. 2022;79(7):645–646. doi:10.1001/jamaneurol.2022.1307 [PubMed: 35666532]
36. Walter S, Taylor A, Tyrone J, et al. Disclosing Individual Results in Dementia Research: A Proposed Study Participant's Bill of Rights. J Alzheimers Dis. 2022;90(3):945–952. doi:10.3233/JAD-220810 [PubMed: 36278354]
37. Roberts JS, Ferber R, Blacker D, Rumbaugh M, Grill JD, Dementia (AGREED) for the AG on REE for. Disclosure of individual research results at federally funded Alzheimer's Disease Research Centers. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2021;7(1):e12213. doi:10.1002/trc2.12213 [PubMed: 34692986]
38. RFA-AG-24–001: Alzheimer's Disease Research Centers (P30 Clinical Trial Not Allowed). Accessed January 22, 2023. https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-24-001.html

39. Best practices | National Alzheimer's Coordinating Center. Accessed May 1, 2023. https://naccdata.org/adrc-resources/best-practices
40. Babulal GM, Quiroz YT, Albensi BC, et al. Perspectives on Ethnic and Racial Disparities in Alzheimer's Disease and Related Dementias: Update and Areas of Immediate Need. Alzheimers Dement. 2019;15(2):292–312. doi:10.1016/j.jalz.2018.09.009 [PubMed: 30555031]
41. Veitch DP, Weiner MW, Aisen PS, et al. Using the Alzheimer's Disease Neuroimaging Initiative to improve early detection, diagnosis, and treatment of Alzheimer's disease. Alzheimer's & Dementia. 2022;18(4):824–857. doi:10.1002/alz.12422
42. Ashford MT, Raman R, Miller G, et al. Screening and enrollment of underrepresented ethnocultural and educational populations in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Alzheimers Dement. 2022;18(12):2603–2613. doi:10.1002/alz.12640 [PubMed: 35213778]
43. Mindt MR, Okonkwo O, Weiner MW, et al. Improving generalizability and study design of Alzheimer's disease cohort studies in the United States by including under-represented populations. Alzheimers Dement. 2023;19(4):1549–1557. doi:10.1002/alz.12823 [PubMed: 36372959]
44. Weiner MW, Veitch DP, Miller MJ, et al. Increasing participant diversity in AD research: Plans for digital screening, blood testing, and a community-engaged approach in the Alzheimer's Disease Neuroimaging Initiative 4. Alzheimers Dement. 2023;19(1):307–317. doi:10.1002/alz.12797 [PubMed: 36209495]
45. Erickson CM, Clark LR, Ketchum FB, Chin NA, Gleason CE, Largent EA. Implications of preclinical Alzheimer's disease biomarker disclosure for US policy and society. Alzheimers Dement (Amst). 2022;14(1):e12339. doi:10.1002/dad2.12339 [PubMed: 36035626]
46. Implications for Behavioral and Social Research of Preclinical Markers of Alzheimer's Disease and Related Dementias: Proceedings of a Workshop–in Brief. National Academies of Sciences, Engineering, & Medicine doi:10.17226/26295
47. Joshi A, Koeppe RA, Fessler JA. Reducing between scanner differences in multi-center PET studies. Neuroimage. 2009;46(1):154–159. doi:10.1016/j.neuroimage.2009.01.057 [PubMed: 19457369]
48. Jagust WJ, Landau SM, Koeppe RA, et al. The Alzheimer's Disease Neuroimaging Initiative 2 PET Core: 2015. Alzheimers Dement. 2015;11(7):757–771. doi:10.1016/j.jalz.2015.05.001 [PubMed: 26194311]
49. Royse SK, Minhas DS, Lopresti BJ, et al. Validation of amyloid PET positivity thresholds in centiloids: a multisite PET study approach. Alzheimer's Research & Therapy. 2021;13(1):99. doi:10.1186/s13195-021-00836-1
50. Largent EA, Bhardwaj T, Clapp JT, Sykes OS, Harkins K, Grill JD. You've Got a Friend in Me: How Cognitively Unimpaired Older Adults Select a Study Partner to Participate with Them in Alzheimer's Disease Research. J Alzheimers Dis. 2022;90(3):1021–1033. doi:10.3233/JAD-220061 [PubMed: 35311710]
51. Raman R, Quiroz YT, Langford O, et al. Disparities by Race and Ethnicity Among Adults Recruited for a Preclinical Alzheimer Disease Trial. JAMA Netw Open. 2021;4(7):e2114364. doi:10.1001/jamanetworkopen.2021.14364 [PubMed: 34228129]
52. Creese B, Ismail Z. Mild behavioral impairment: measurement and clinical correlates of a novel marker of preclinical Alzheimer's disease. Alzheimers Res Ther. 2022;14(1):2. doi:10.1186/s13195-021-00949-7 [PubMed: 34986891]
53. Ryff CD, Keyes CL. The structure of psychological well-being revisited. J Pers Soc Psychol. 1995;69(4):719–727. doi:10.1037//0022-3514.69.4.719 [PubMed: 7473027]
54. van Dierendonck D The construct validity of Ryff's Scales of Psychological Well-being and its extension with spiritual well-being. Personality and Individual Differences. 2004;36(3):629–643. doi:10.1016/S0191-8869(03)00122-3
55. Boyle PA, Buchman AS, Wilson RS, Yu L, Schneider JA, Bennett DA. Effect of Purpose in Life on the Relation Between Alzheimer Disease Pathologic Changes on Cognitive Function in Advanced Age. Archives of General Psychiatry. 2012;69(5):499–504. doi:10.1001/archgenpsychiatry.2011.1487 [PubMed: 22566582]

56. Boyle PA, Barnes LL, Buchman AS, Bennett DA. Purpose in Life Is Associated With Mortality Among Community-Dwelling Older Persons. Psychosom Med. 2009;71(5):574–579. doi:10.1097/PSY.0b013e3181a5a7c0 [PubMed: 19414613]

57. Largent EA, Bhardwaj T, Abera M, et al. Disclosing Genetic Risk of Alzheimer's Disease to Cognitively Unimpaired Older Adults: Findings from the Study of Knowledge and Reactions to APOE Testing (SOKRATES II). J Alzheimers Dis. 2021;84(3):1015–1028. doi:10.3233/JAD-210675 [PubMed: 34602479]

58. Yesavage JA, Sheikh JI. 9/Geriatric Depression Scale (GDS). Clinical Gerontologist. 1986;5(1–2):165–173. doi:10.1300/J018v05n01_09

59. van Marwijk HW, Wallace P, de Bock GH, Hermans J, Kaptein AA, Mulder JD. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. Br J Gen Pract. 1995;45(393):195–199. [PubMed: 7612321]

60. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med. 1979;41(3):209–218. doi:10.1097/00006842-197905000-00004 [PubMed: 472086]

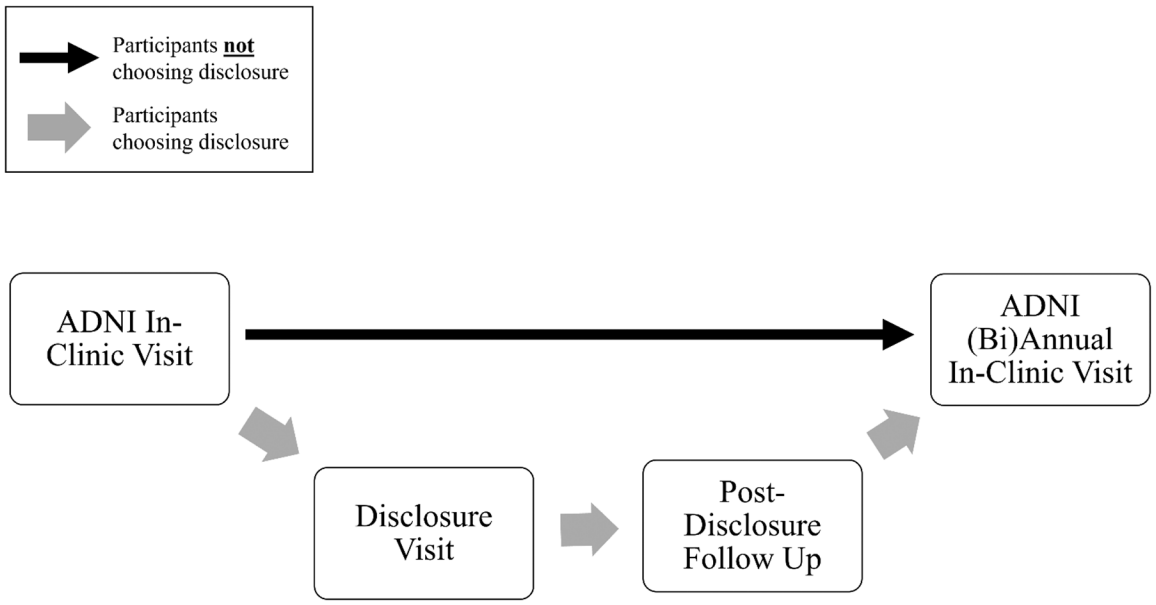

Figure 1.

ADNI visit flow with disclosure visits. Participants opting to learn their amyloid PET results will complete two study visits in addition to the standard in-clinic ADNI visits. In-clinic visits can include a physical exam, neuropsychological exam, and amyloid PET scan depending on the participant's cognitive status and progress in study. The pre-disclosure visit will be conducted at the ADNI in-clinic visit. Participants will have the opportunity to learn the results of all amyloid PET scans conducted throughout the duration of the study.

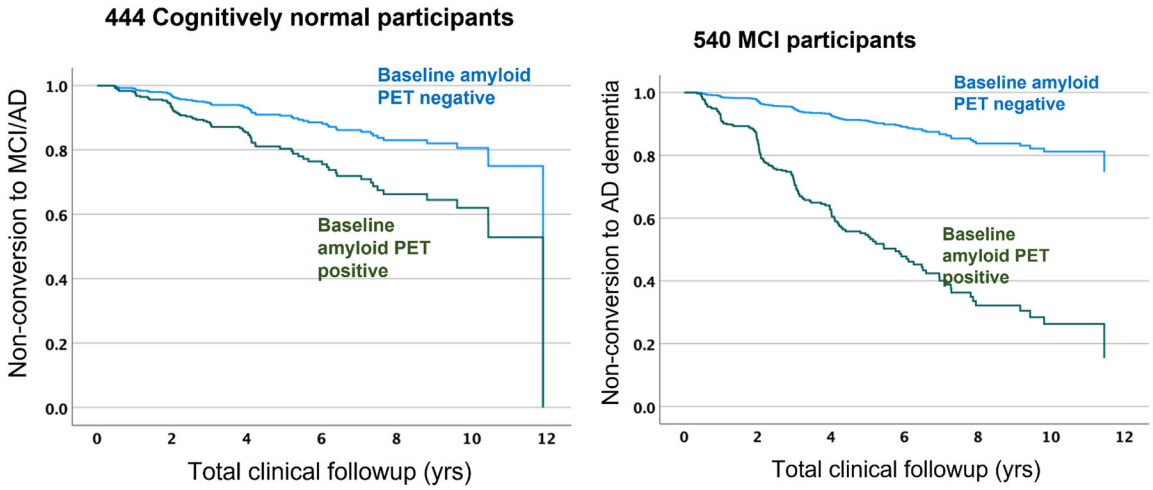

Figure 2.

Relative risk curves included in the participant education material and investigator training manual. (Left) Survival curves for cognitively unimpaired ADNI participants for the outcome of conversion to an MCI or dementia diagnosis over 5.1 +/− 4.0 years of post-amyloid PET clinical follow up. Cognitively unimpaired participants who were amyloid elevated at baseline were 2.2 times more likely to convert to an impaired diagnosis compared to participants with not elevated amyloid. (Right) Survival curves for participants with MCI at baseline for the outcome of conversion to a dementia diagnosis in clinical follow up over 5.1 +/− 4.0 years. Participants with MCI at baseline who demonstrated elevated amyloid were 6.4 times more likely to convert to a dementia diagnosis than participants with not elevated amyloid.

Table 1.

Visit Measures

	In-Clinic ADNI Visit ~12 weeks pre-disclosure	Disclosure Visit	Post-Disclosure Follow-Up ~1-week post-disclosure	(Bi)Annual ADNI Visit(s) ~1-year post-disclosure
Previous knowledge of amyloid result	X			
Ryff Psychological Well-Being Purpose in Life subscale	X			X
Anticipated result and confidence with estimate	X			
Perceived risk of dementia *(only for unimpaired and MCI participants)*	X		X	X
Geriatric Depression Scale-15 Items	X	X*		X
Mini State Trait Anxiety Inventory*		X*		
Columbia Suicide Severity Rating Scale*		X*		
Clinician rating of participant understanding and emotional response		X		
Clinician report of disclosure visit (topics discussed, challenges encountered, confidence)		X		
Impact of Events – Intrusion and Avoidance subscales			X	X
Recall of Amyloid Result			X	X
Comprehension of Amyloid Result			X	X
Participant Value of Learning Result			X	X
Participant Satisfaction with Disclosure			X	
Who Participant Shared Result With			X	
Post-Disclosure Behavior Changes				X

* -Optional, administered based on clinician discretion