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Biomarker disclosure protocols in prodromal Alzheimer's disease clinical trials

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Abstract

INTRODUCTION: The development of biomarkers for Alzheimer's disease (AD) has allowed researchers to increase sample homogeneity and test candidate treatments earlier in disease. The integration of biomarker 'screening' criteria should be met with parallel implementation of standardized methods to disclose biomarker testing results to research participants; however, the extent to which protocolized disclosure occurs in trials is unknown.

METHODS: We reviewed the literature to identify prodromal AD trials published in the past 10 years. From these, we quantified frequency of biomarker disclosure reporting and depth of descriptions provided.

RESULTS: Of 30 published trials using positron emission tomography or cerebrospinal fluid-based amyloid positivity as an eligibility criterion, only one mentioned disclosure, with no details on methods.

DISCUSSION: Possible reasons for and implications of this information gap are discussed. Recommendations are provided for trialists considering biomarker screening as part of intervention trials focused on prodromal AD.

Keywords

Prodromal Alzheimer's disease; Mild Cognitive Impairment; Randomized Controlled Trials; Amyloid; Biomarker Disclosure

1. Introduction

The development of biomarkers for Alzheimer's disease (AD)[1] has accelerated progress towards early detection and novel treatments. Biomarker-characterized individuals with mild cognitive impairment (MCI)[2] or prodromal AD[3] (i.e., those with amyloid positivity, mild

symptoms, but functional independence) are increasingly the focus of trials that seek to intervene earlier in the disease process[4]. Manuscripts arising from these trials often describe details of biomarker selection, acquisition, and analysis; conversely, whether and how AD biomarker results are disclosed to participants is unknown.

The careful disclosure of biomarker results has implications not only for trial recruitment[5], but also for the participant's physical and psychological health. While instances of actual medicolegal discrimination (e.g., loss of access to long-term care insurance or medical procedures secondary to biomarker positivity) are rarely reported, this phenomenon is difficult to measure and therefore understudied[6]. In light of the at-least theoretical risk of discrimination, advocates have called for a Biomarker Information Non-Discrimination Act[7] analogous to the Genetic Information Non-Discrimination Act, to protect participants and patients against this risk. Additional risks of biomarker disclosure include elevated psychological distress and experiences of stigma within one's family or community. Perhaps most troublesome is evidence that many participants enrolled in clinical AD research are unaware of or underestimate these risks[8]. In contrast, biomarker results shared with providers may support diagnostic confidence[9,10], and personalized health and lifestyle change for participants[11]. Participants and their loved ones may also leverage biomarker data to plan for the future and prepare for caregiving roles[12]. Given growing evidence of the impact of learning biomarker results, it is critical to understand whether and how prodromal trials are incorporating and reporting biomarker disclosure.

2. Methods

To investigate how prodromal AD trials disclose biomarker results, authors ARF and LRC conducted a literature review through independent, systematic searches using PubMed. Given the relative recency of biomarker implementation, we restricted search criteria to randomized controlled trials published between 01/2013 and 02/20/23. Search terms included "prodromal Alzheimer's disease" [48 results], "mild cognitive impairment AND Alzheimer's disease AND amyloid" [70 results], and "dementia AND Alzheimer's disease AND amyloid" [199 results]. Consistent with Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines, we screened the abstracts, methods, and references. Only trials using position positron emission tomography (PET) or cerebrospinal fluid (CSF) amyloid biomarkers were included; trials implementing more exploratory biomarkers were excluded, as there is no expectation for disclosure of such test results. Additionally, only trials that utilized biomarkers as part of eligibility screening were included, while studies with biomarker covariates or outcomes were not. All trials that included a prodromal AD and/or MCI group were included, even if participants at other stages of the disease were also included. However, studies focused solely on cognitively healthy individuals or those with dementia were excluded from review. All reviewed trials were written in English. This review identified 30 published trials that included participants with prodromal AD and positive PET or CSF amyloid biomarkers as formal inclusion criteria (see Figure 1). Scrutiny of these articles sought to quantify how many (a) mentioned biomarker disclosure, (b) detailed the disclosure process, and (c) referenced a specific protocol for disclosure. A complete summary of manuscripts reviewed is available in the Supplemental material.

3. Results

Only one (<3%) of 30 prodromal AD trial manuscripts[13] mentioned biomarker disclosure, and only when discussing how ineligible participants were handled. No study provided details of disclosure (e.g., disclosure providers, standardized language, audiovisual materials, safety monitoring) in the publication or associated supplemental materials.

4. Discussion

Our review of biomarker disclosure practices within the relatively nascent field of prodromal AD trials was restricted by a near total absence of disclosure information in available manuscripts. There may be many reasons for this omission. The development and dissemination of research protocols for communicating biomarker results has lagged behind biomarker development[14]. To date, no practice guidelines exist for disclosure, which may falsely imply that disclosure is a minor step in the screening process that does not necessitate formal documentation of methodology. Additionally, disclosure training resources are lacking, potentially implying that no training is required. However, the growing literature supports the need for pre- and post-disclosure counseling (and, when appropriate, decisional capacity assessment), screening for psychological stability before and following disclosure, and careful delivery of standardized messaging by a trained clinician investigator[15].

This preliminary review of the literature raises several important concerns. First, **studies are not routinely reporting biomarker disclosure methods**. Secondly, this paucity in reporting raises concern that **some studies may not disclose biomarker results to potential participants**. Return of research results to participants with prodromal AD is increasingly common[16,17], given that individuals in this intermediate clinical ‘zone’ may benefit most from early intervention and care. Investigators may be prohibited from sharing biomarker results in circumstances in which disclosure may confound trial outcomes or when the biomarker validity remains uncertain; however, neither are likely to be the case in prodromal AD trials using amyloid biomarkers. Concerns that biomarker disclosure could result in participants being forced to receive unwanted results have led to the use of “blinded” trial designs on ethical grounds. These concerns are largely unfounded; analysis of relative risks and benefits of disclosure do not indicate that coercion or undue influence occur in cases of pre-randomization disclosure[18]. Furthermore, studies have demonstrated that required biomarker disclosure is not a significant barrier to recruitment[19] and does not impact willingness to engage in future AD research even when a participant is excluded for biomarker ineligibility[5]. On the contrary, participants and care partners may be more motivated to enroll in trials providing this feedback[20].

A third concern is that **unstandardized return of biomarker results may yield inconsistent effects for participants and families**. Data from trials implementing empirically supported and standardized disclosure protocols suggest that cognitively symptomatic[21] and asymptomatic individuals[22] tolerate learning their amyloid results well. However, amyloid positive individuals and their care partners may still experience heightened distress, and amyloid negative individuals report greater confusion about their MCI diagnosis post-disclosure[23]. Though relatively low probability when standardized

disclosure protocols are used, these risks may be significantly exacerbated in cases wherein disclosure across study arms is inconsistent in structure or style, unclear, or deficient in post-disclosure support. Conversely, prodromal amyloid positive individuals may also use their biomarker results to enact health behavior changes such as initiating treatments, improving diet or physical activity, assisting with caregiver preparation, and planning for health and finances[24]. Unstandardized or inappropriate disclosure may reduce these potential positive impacts.

A final concern is that **unstandardized disclosure of results may have an impact on trial outcomes and safety**. As previously noted, disclosure has variable consequences. While randomization may disperse risk for adverse events evenly between treatment arms, these events – which might otherwise have been avoided – may still occur. Inconsistent disclosure may also cloud interpretation of enrollment numbers, drop-out, and even outcomes, particularly if there is variability in approach by site. Disclosure-mediated stereotype threat may also impact behavioral or cognitive outcomes[25]; if variable disclosure strategies result in variable threat, these effects could be unequally distributed in treatment arms or among sites.

Ultimately, failure to consistently implement, evaluate, and summarize results of disclosure greatly limits generalization and translation of biomarker disclosure practices across studies.

5. Recommendations

Based on the findings of our literature review and the ethical and practical implications listed above, we provide the following recommendations (Table 1):

1. *Prodromal AD trials using established methods for amyloid screening should routinely include protocols for results disclosure to participants.* Several disclosure protocols and toolkits are now published[15,22, 23,26–27]. Ideally, protocols would define (a) how informed consent describes risks and benefits of *disclosure* (in addition to risk/benefits of the intervention); (b) participant suitability criteria for disclosure and how they are assessed, (c) methods and timeline for disclosing results; (d) study team qualifications, training, and roles in disclosure; (e) disclosure messaging (i.e., how positive or negative results are conveyed); and (f) post-disclosure monitoring and resources. Furthermore, researchers should define methods and pathways for *all* participants, regardless of trial eligibility or enrollment (e.g., those who are biomarker positive but otherwise ineligible for the trial; those who are biomarker negative and trial ineligible, but symptomatic).

2. *Post-disclosure safety and tolerability data should be collected independently from data related to the safety of the experimental intervention.* Although disclosure has been found to be relatively safe, it is not without impact. Furthermore, few studies have explored the impact of disclosure within an existing trial. For instance, if baseline mood assessment is conducted only pre-disclosure for the purpose of screening, the research team may not ‘catch’ individuals who experience post-disclosure distress. Disclosure-driven adverse

events would likely occur at equivalent rates across study arms due to randomization; however, safety and drop-out may be affected if post-disclosure reactions are not adequately considered. These data would also be instructive for future clinical practice in which biomarker-informed diagnosis and treatment will likely be standard of care.

3. *Researchers should identify resources for participants and study partners to gain post-disclosure support outside of the trial*. While it is likely beyond the scope of most trials to formally assess the impact of disclosure beyond the participant, research suggests that those poised for caregiving roles are also affected by amyloid results[28]. These risks and benefits may be part of informed consent discussions. Studies may consider collating resources for participants and study partners to acquire follow-up educational information and, if needed, supports and clinical care.

4. *Biomarker disclosure protocols within prodromal trials should be disseminated as part of, or supplemental to, other trial results.* Beyond the impacts of disclosure on participants and the downstream effects for trial results, prodromal trial biomarker disclosure practices should be protocolized and published on the grounds of open science. The investigative team should share not only how disclosure was accomplished, but also any safety and tolerability data associated with this protocol. This approach would allow for systematic comparison of methods to 'dismantle' necessary or risky/harmful elements of disclosure for future studies. Furthermore, detailed descriptions of disclosure increase rigor and reproducibility of these methods in future work and inform best practices.

5. *Best practice guidelines for integrating disclosure of amyloid (and eventually other AD biomarkers) into clinical trials are needed.* This task will require significant interdisciplinary effort within the ADRD community. While various groups, including the Advisory Group on Risk Evidence Education in Dementia (AGREED)[29], have begun to develop approaches and share resources, a unified and funded effort will be important to fully realize this goal. Researchers may follow the example of prior work on the development of practice guidelines for genetic disclosure in clinical trials[30] as well as ongoing work in investigating and developing optimal communication strategies and personalized biomarker result tools[31–33].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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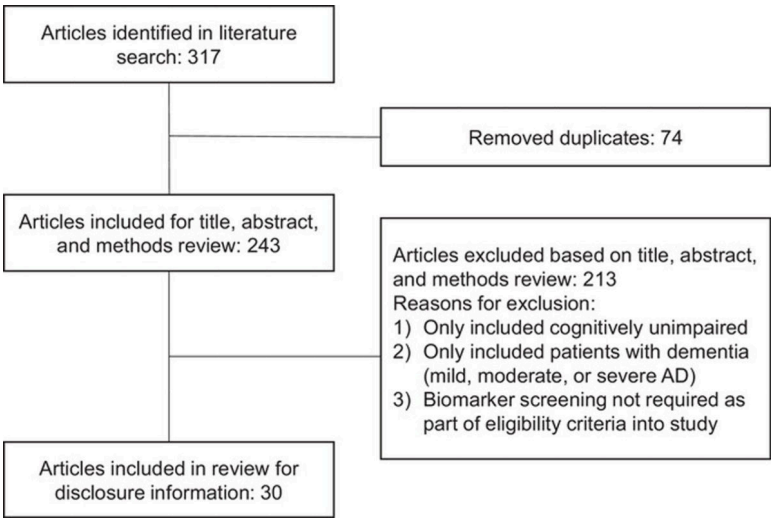

Figure 1.
PRISMA Diagram of Literature Review.

Table 1.

Recommendations for Biomarker Disclosure within Prodromal AD Trials

• Researchers should develop protocols for biomarker disclosure prior to trial initiation, including: – Methods and timeline for disclosure to participants – Study team roles and training – Discussion of disclosure risks/benefits in informed consent – Standardized disclosure messaging and graphics – Post-disclosure safety assessments – Post-disclosure educational and support resources for patients and loved ones
• The study team must define follow-up pathways for all participants, regardless of biomarker result and trial eligibility
• The impact of post-disclosure reactions on trial eligibility and results should be considered
• Authors should discuss or reference disclosure protocols as part of all trial publications
• Best practice guidelines for integrating amyloid disclosure into clinical trials are needed