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# Ethical Frameworks for Disclosure of Alzheimer Disease Biomarkers to Research Participants: *Conflicting Norms and a Nuanced Policy*

Eline M. Bunnik, Marthe Smedinga, Richard Milne, Jean Georges, Edo Richard, and Maartje H. N. Schermer

**ABSTRACT** More and more frequently, clinical trials for Alzheimer disease (AD) are targeting cognitively unimpaired individuals who are at increased risk of developing the disease. It is not always clear whether AD biomarker information should be disclosed to research participants: on the one hand, research participants may be interested in learning this information because of its perceived utility, but on the other hand, learning this information may be harmful, as there are very few effective preventive or therapeutic options available for AD. In this article, we bring together three separate sets of ethical guidance literature: on the return of individual research results, on an individual's right to access personal data, and on transparent enrollment into clinical trials. Based on these literatures, we suggest policies for the disclosure of AD biomarker test results in longitudinal observational cohort studies, clinical trials, and hybrid research projects, such as the European Prevention of Alzheimer's Dementia (EPAD) project, in which we served as an ethics team. We also present and critically discuss recommendations for disclosure of AD biomarkers in practice. We underscore that, as long as the clinical validity of AD biomarkers remains limited, there are good reasons to avoid actively disclosing them to cognitively unimpaired research participants.

**KEYWORDS** human subjects research, human research ethics, Alzheimer disease, Alzheimer disease biomarkers, returning research results

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Clinical trials for Alzheimer disease (AD) are increasingly focused on intervening in earlier or at-risk stages of disease in the hope of preventing or delaying the onset of dementia. For such trials, recruitment is aimed at finding individuals with limited or no cognitive symptoms who are in an early stage of the disease or at risk of developing it. Risk status is often determined based on either genetic or biomarker testing. For AD, biomarkers can be assessed in cerebrospinal fluid (and in the future, possibly also in blood) or through imaging of the brain, using PET scans, for example.[1] AD is associated with elevated tau levels in cerebrospinal fluid and beta amyloid plaques in the brain as shown on PET scans. When used to predict a healthy individual's future risk of developing the disease, however, the clinical validity of AD biomarkers is limited. Moreover, there are no effective disease-modifying treatment or prevention options available for AD. As AD biomarker information is neither certain nor actionable, learning about these biomarkers may be harmful and burdensome for some research participants who do not have cognitive symptoms.



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At the same time, research participants may be interested in learning whether they are at increased risk of developing the disease, and may actively ask for AD biomarker test results. Participants enrolled in longitudinal observational studies, for instance, may wish to access individual research results pertaining to AD, and researchers may feel obliged to disclose this information. This may also occur, for instance, when cognitively healthy individuals who participate in observational cohort studies are invited to participate in clinical trials of pharmaceutical interventions, as they may be invited on the basis of AD biomarkers information. During the recruitment process, researchers are expected to be transparent toward prospective research participants and to disclose information relevant to the informed consent process, including information about the reasons that individuals were invited to enroll in a clinical trial or other type of research study. This implies that prospective research participants may need to be informed about biomarkers indicating increased risk of developing AD. Researchers are thus confronted with an ethical dilemma: should they inform prospective research participants about AD biomarkers in light of transparency and other informational requirements, when the clinical validity and utility of such biomarkers are limited and doing so may also be harmful to research participants?

In recent years, several large research projects have been set up to enroll and monitor cognitively unimpaired research participants who are at risk of developing AD. These projects include observational studies and registries, clinical trials, and hybrid projects, such as the Global Alzheimer's Platform (GAP) and the European Prevention of Alzheimer's Disease (EPAD) project. The GAP is a patientcentric network of over 90 clinical sites involved in AD research across Northern America aimed at reducing the time investment and costs of AD clinical trials,[2] inter alia by "pre-recruiting" research participants. Its aim is to gather a "trial-ready" cohort of research participants who can be easily enrolled in preclinical or prodromal AD clinical trials.[3] The EPAD project ran from 2016 to 2020 and was funded by the Innovative Medicines Initiative,[4] and we were involved in this project as an ethics team, conducting qualitative and conceptual research and offering ethical guidance throughout the project. The EPAD project combined a longitudinal observational study with a planned platform for clinical trials aimed at accelerating drug development for the prevention of AD.[5] In the past, AD clinical trials had faced several methodological and practical hurdles, including high screening-failure rates[6] and study lengths hindering recruitment and retention of research participants, as well as problems in relation to generalizability of study results. To address these issues, the EPAD project set up a multinational longitudinal cohort study spanning several European countries for the purposes of disease modelling and clinical trial recruitment.[7] Participants with low and high risk of developing AD were recruited from existing population-based and clinical cohorts across Europe and included in the longitudinal study. The aim was to develop and monitor over time a population of healthy individuals and individuals with mild cognitive impairment who were at risk of developing Alzheimer's dementia and who were willing and ready for participation in phase II clinical trials of new compounds—to establish a so-called readiness cohort. From the readiness cohort, investigators could select and invite participants known to have AD biomarkers indicating increased risk of dementia and avoid the trouble of setting up for each trial time-consuming and costly recruitment and screening processes, which are associated with high screening failures.[8] By combining a longitudinal study with a clinical trial platform, the EPAD project aimed at avoiding needless burdens on potential research participants and reducing the costs of recruitment and prescreening. As a consequence of this research design, the EPAD project

**Three sets of ethical guidance—ethics of the return of individual research results, ethics of access to personal data, and ethics of clinical trial enrollment—all pertain to the dilemma at hand: should AD biomarkers be disclosed to cognitively unimpaired research participants?**



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was confronted with questions of whether, when, and how to inform participants about AD biomarkers.

To be able to identify and recruit research participants who are at risk of developing AD dementia for AD prevention or early-intervention studies, people who are (largely) cognitively healthy must be prescreened for increased risk of the disease by assessing AD biomarkers. Cognitively healthy research participants in whom, for instance, abnormal amyloid beta levels have been detected may be labeled positive for AD biomarkers. People with no symptoms of AD dementia and with positive results from AD biomarker testing are currently referred to by some as having preclinical AD[9] or even as having AD.[10] Following these classifications, recruitment for AD prevention studies may turn cognitively healthy people into people with a diagnosis of (preclinical) AD if they test positive on AD biomarkers. It was recently suggested that diagnosis of AD should be reserved for individuals with AD phenotypes and that biomarker-positive individuals who are cognitively unimpaired should be considered at-risk for progression to Alzheimer disease.[11]

Yet the predictive value of AD biomarkers for the development of AD is uncertain, particularly in people without objective cognitive impairment,[12] and increasingly so with age.[13] The predictive value is highly dependent on the (age) cohort in which it is investigated, with five-year progression rates in persons without amyloid-beta depositions ranging roughly from 15% to 50% and with amyloid-beta depositions ranging roughly from 35% to 70%.[14] Particularly in older age groups, the competing risk of mortality due to other causes should also be taken into account. Consequently, a high level of uncertainty remains around any prediction of progression to AD, rendering the clinical utility of these biomarkers for individual patients low. Thus, in cognitively unimpaired individuals, AD biomarkers cannot be used to distinguish reliably between those who will and those who will not develop the disease. In the clinic, AD biomarker tests are therefore generally not considered suitable for use in people with only subjective cognitive symptoms. Thus, prominent clinical guidelines recommend against the routine use of AD biomarker tests in clinical practice, especially in people without objective cognitive impairment.[15]

Research participants, however, may be interested in receiving the results of AD biomarker tests and may see feedback about such results as a benefit of research participation rather than a burden. Empirical studies of research participants' perspectives suggest that AD biomarker disclosure is not seen as a barrier to enrollment.[16] In fact, research participants wish to learn about AD biomarkers and tend to attribute value to the result of amyloid testing, even compared to other medical tests.[17] One important reason for this is that, despite the lack of clinical utility given the paucity of treatment options, participants feel that AD biomarkers may have personal utility.[18] They may think that knowing their AD risk status may help them to effect life changes and prepare themselves and their loved ones—both mentally and practically—for a future with AD.[19] They may also feel that it gives them the opportunity to set up advance directives, make arrangements for long-term care and support, and even consider euthanasia.[20] All this personal utility may be attributed to AD biomarkers even if research participants are clearly informed by study doctors that such biomarkers or their apparent absence only increases or decreases their risk and that the doctors are far from certain about whether they will develop AD.

In this article, we discuss the ethical dilemma of disclosure drawing on three distinct bodies of ethical guidance literature, which have developed separately and may offer different, even conflicting, recommendations for the disclosure of AD biomarkers in different research contexts. Then, we detail how, on the basis of these literatures, we gave shape to the disclosure policy of the EPAD consortium, and we discuss the tensions it gave rise to. Finally, we draw on our experiences in the EPAD consortium to offer recommendations for the disclosure of biomarkers, information provision, and the informed consent process. These recommendations can be used by other research groups involved in the design or conduct of hybrid studies or clinical trials in which recruitment is based on biomarker data and by research ethics review boards tasked with evaluating such research.

## ETHICAL FRAMEWORKS FOR DISCLOSURE OF AD BIOMARKERS

Three sets of ethical guidance—ethics of the return of individual research results, ethics of access to



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personal data, and ethics of clinical trial enrollment—that arose and have evolved independently from one another, being developed in bodies of literature, all pertain to the dilemma at hand: should AD biomarkers be disclosed to cognitively unimpaired research participants?

**Ethics of the return of individual research results.** While researchers have an ethical obligation to return aggregate results of medical research studies involving human research participants,[21] they have traditionally not had any obligation to actively return individual research results. However, "the justification for returning results becomes stronger as both the potential value of the result to participants and the feasibility of return increase."[22] In the context of genetics and genomics research, there has been considerable and long-standing debate on the value of disclosing individual research results to research participants.[23] There is a growing consensus that researchers should offer feedback of *relevant* genetic or genomic research results to research participants.[24] However, it may be difficult for researchers to determine whether individual research results are relevant. It is not always clear "when results must, should, may, or must not be returned."[25] Most policies use three criteria to determine whether feedback is warranted:[26] analytical validity, clinical significance (or clinical validity), and actionability (or clinical utility). Individual research results should be returned to research participants when they accurately establish the presence or absence of a genetic variant (satisfying the criterion of analytical validity), when this variant is reliably associated with a meaningful increase in risk of disease (clinical validity), and when the disease can be prevented or treated using acceptable and available methods (clinical utility). The rationale is that research participants can benefit from learning about individual research results only if those results reliably establish a (present or future) medical problem that can be acted upon.

Application of these three criteria to AD biomarker research results raises several concerns. First, there are concerns about the clinical validity of the information. Given the uncertainty surrounding the clinical significance of AD biomarkers in cognitively unimpaired individuals, disclosure of such information is generally not recommended. Disclosure of AD biomarkers may place "a cloud of uncertainty over participants."[27] Labeling of cognitively healthy research participants with AD biomarkers as having preclinical AD may lead to misunderstandings.[28] Because AD biomarkers in cognitively unimpaired individuals cannot be meaningfully interpreted, they should not be disclosed.[29]

Second, disclosure of AD biomarkers lacking clinical validity or utility might harm cognitively unimpaired research participants. These individuals may unduly come to believe—especially if they go on to read about AD biomarkers on the internet—that they are now ill or will inevitably become ill. The image of the Sword of Damocles is often used as an illustration of the continuous fear and burden that may arise when knowing one's fate. Thus far, however, the limited empirical evidence suggests that the quantifiable psychological impact of AD biomarker disclosure on cognitively healthy research participants is generally low.[30] A recent overview of the literature on the impact of disclosure on research participants concludes that AD biomarker disclosure is safe in this population.[31] However, as current empirical research on the impact of AD biomarker disclosure is mostly quantitative in nature, measuring effects using depression and anxiety scales, it may fail to capture more subtle psychological and social effects. It is also limited in terms of the populations for whom evidence is available. Learning that one has AD biomarkers may have negative implications for identity, self-determination, and stigma,[32] for instance, and may lead to hypervigilance toward cognitive (dys)functioning in daily life.[33] This knowledge may also adversely affect research participants' cognitive performance.[34] One study found, for instance, that older, cognitively unimpaired adults who knew their at-risk *APOE*-genotype performed worse in objective memory tests and had lower subjective estimations of their memory compared to those who were at risk but were not aware of that risk.[35] Such potential adverse impacts are disconcerting, especially in light of the limited ability of AD biomarkers to estimate future risk of AD, which renders many of these impacts false or unnecessary.

Third, in the context of AD, these harmful or wrongful impacts cannot be offset by any potential benefits, medical or otherwise. Often, it is claimed that disclosure of AD biomarker information may result in "potential benefits to the individual, including bolstered autonomy."[36] It could prompt individuals to make changes



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in their personal or professional lives or take up long-term-care insurance or long-term-care plans. However, if these actions are motivated by false belief (i.e., the belief that one will develop AD while this is not the case, or at least not certain at all), individual autonomy is not promoted.[37] Would it be sensible to make important life changes for a 75-year-old woman without cognitive impairment, for instance, based on the knowledge that she has a 23.5% lifetime risk of developing Alzheimer disease, given her abnormal amyloid beta levels, instead of a 13.8% risk, like that of others of similar age with normal amyloid beta levels?[38] In this case, the perceived personal utility of AD biomarker information may be the result of a misunderstanding if the 75-year-old person believes that she will develop AD dementia or has a high risk of doing so. In addition, with an undue focus on AD biomarkers, individuals may lose sight of other risk factors for AD, including age, cardiovascular health, genotype, and diet, some of which may be more important, and some of which may be modifiable. The biomarker alone does not distinguish those who will develop the disease from those who will not. When risk information is highly uncertain (has little clinical validity), it is not useful, not even personally—and it had better not be used.[39] Until there is clinical validity in AD biomarker test results, there may not be a way for cognitively unimpaired research participants to attain any medical or personal benefit to outweigh potential harms of learning that they have tested positive for such biomarkers.

Fourth, even if adopting healthier lifestyles or making positive life changes in response to biomarker test results does not actually harm research participants,[40] and might even benefit them, their doing so on the basis of unfounded (and bleak) projections of their future cognitive health is not right. Putting research participants in the position of making life(style) changes on the basis of false information conflicts with the principle of respect for autonomy. This also applies to the substantial life-planning changes, such as moving houses or changing jobs, that cognitively healthy research participants have reported considering after receiving positive biomarker results.[41] Only on the basis of reliable information can human beings give shape to their lives in meaningful ways, and in accordance with their personal values.

Thus, disclosing findings about AD biomarkers is not in line with established criteria—analytical validity, clinical validity, and clinical (or, for that matter, personal) utility—put forward in the ethics literature on the return of individual research results, nor with the medical-ethical principles of beneficence, nonmaleficence, and respect for autonomy.[42] Based on the ethics of the return of individual research results, AD biomarkers should not be routinely offered to members of cognitively unimpaired research populations involved in observational AD studies.

**Ethics of access to personal data.** It is acknowledged increasingly often that individuals have a right to access to data about themselves that is collected by others. A right to access and control of one's personal data follows from fundamental rights and freedoms, including the right to informational self-determination and privacy.[43] In Europe, a legal right to access health-related data is supported by several legal frameworks. The Convention on Human Rights and Biomedicine of the Council of Europe, for instance, states that "everyone is entitled to know any information collected about his or her health."[44] Importantly, the European Union's recently implemented General Data Protection Regulation (GDPR) contains a right for the "data subject" to access any personal data held by a "controller" (see article 15 of the GDPR), including health data or biomedical data collected for research purposes.[45] Research participants do not have a legal right to access research data about themselves in all jurisdictions around the world,[46] yet it is broadly acknowledged that research participants have a prima facie moral right to access such data.[47] When research participants take the initiative to ask for it, they should be given access to research data relating to themselves.

With increasing frequency, it is suggested that researchers should not wait for research participants to make explicit requests but should take the right to access as a starting point and honor that right more proactively. Accordingly, more recent guidance leans toward the communication of results.[48] Such guidance takes its cues from community-engaged and participatory approaches to research and supports more open and bidirectional data exchange and communication between researchers and research participants.[49] Research groups that routinely disclose AD biomarker test results



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to cognitively healthy research participants cite participants' preferences, empowerment, and reciprocity as reasons for doing so.[50] Some commentators expect that, in line with this view, more and more studies will routinely or actively share AD biomarker test results with research participants.[51]

Ideally, however, research data should be returned in a manner that is understandable to the research participant and that minimizes any risks associated with disclosure. After all, learning about uncertain and/or difficult-to-interpret research data might be harmful to research participants. Sufficient resources should be available[52] to conduct additional analyses or confirmatory testing and to provide medical or psychosocial services, such as counseling, to ensure the welfare of research participants when disclosing research results. There are concerns that ethically responsible data access may not always be feasible in practice.[53] The "effort involved in re-contacting participants and returning results in ways that are responsible and likely to be useful to them can be significant."[54] When confronted with a request from a research participant to learn individual research results, the researcher need not grant the request immediately, but may engage in a discussion about purposes, limitations, benefits, and risks of disclosure. Therefore, researchers might discourage research participants from pursuing access to research data. Studies have shown that when research participants understand that the reliability and actionability of AD biomarkers are currently limited, their interest in learning this information decreases.[55] During the informed consent process, researchers might inform research participants that—for instance, because of limited resources—access to research data will not be provided. Ultimately, however, ethical and legal frameworks for access to personal data imply that if a research participant has a well-considered and persistent wish to access research data, the researcher should accommodate that wish, even if this requires time and effort.

Thus, research participants have a right to learn about AD biomarkers upon their explicit request. Although the ethics of access to personal data does not require researchers to share data actively or routinely with research participants, it does require them to disclose data when research participants ask for it.

**Ethics of clinical trial enrollment.** The ethical requirement of transparency about clinical trial enrollment began with *The Belmont Report* in the late 1970s.[56] Ever since, respect for persons has been a fundamental ethical principle in medical research involving human subjects. Respect for persons entails that the autonomy or capacity "of deliberation about personal goals and of acting under the direction of such deliberation" of individuals must be acknowledged.[57] That is, the considered decisions of autonomous research participants must be respected. Research participants should enter into research voluntarily and on the basis of adequate information. Withholding information that is necessary to make considered decisions—in the form of informed consent to research participation—is wrong. *The Belmont Report* lists "items for disclosure intended to ensure that subjects are given sufficient information," such as the purpose of research, risks and benefits, alternatives, and the right to withdraw at any time, and mentions "[a]dditional items," including "how subjects are selected."[58]

AD biomarkers currently have limited predictive value and cannot answer the most common question of research participants in AD prevention studies: whether they will or will not develop dementia. This is the key message to be conveyed and reiterated during information provision, informed consent, and ongoing communication processes within AD research studies.

The recommendation to inform prospective research participants about how they were selected has been incorporated in the authoritative guidelines of the Council for International Organizations of Medical Science for health-related research involving humans.



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Article 8 of these guidelines states that participants in clinical trials must be informed about the reason they were invited to take part.[59] In the literature, this is referred to as "transparent" enrollment.[60] When prospective research participants are recruited for a clinical trial based on individual-level AD biomarker results, transparent enrollment occurs if they are informed that they were invited to participate on this basis. In clinical trials that are open only to research participants who have AD biomarkers, disclosure is, in fact, already inherent in the participant screening process: those who test negative for AD biomarker tests will not be invited to take part in the trial. For this type of trial, disclosure of AD biomarkers thus takes place as a routine part of a transparent enrollment process.

Transparent enrollment is contrasted with blinded enrollment. For some time, blinded enrollment was deemed preferable[61] in light of the above-mentioned risks of harm associated with AD biomarker disclosure but also to avoid potential bias in memory testing, which was sometimes the main outcome measure in AD clinical trials. Moreover, to individuals who do not wish to learn about their AD biomarkers, routine disclosure as part of a transparent enrollment process might be unwanted and potentially coercive. Persons who are not willing to learn their AD biomarker status might be pressured to accept disclosure in order to be able to enroll in the trial. However, Kim et al. argue that, as individuals who do not wish to learn their AD biomarker status are probably not attracted to such a research project, a right to participate in a clinical trial does not exist, and individuals are free to choose not to take part, coercion does not occur.[62]

The use of blinded enrollment might imply that larger numbers of participants are needed—and thus exposed to the risks and burdens of research participation—to achieve the aims of the research project. Interventional AD studies are commonly meant to answer research questions regarding the effects of drug treatments on AD biomarkers as proxies for clinical outcomes. In such studies, biomarker-negative individuals would be invited only so that researchers could inform them that being invited to the trial does not mean that they are biomarker-positive and, thus, to maintain uncertainty regarding the AD biomarker status of individual participants (to protect them against any harms resulting from disclosure). The inclusion of biomarker-negative participants would act only as a decoy and would not be required to answer the research question. Enrolling and exposing healthy volunteers to risks only to avoid "disclosure by enrollment" in others would be disproportionate and arguably unethical—and a waste of resources.[63] To protect biomarker-negative individuals from the risks and burdens associated with (unnecessary) research participation, for interventional AD studies, transparent enrollment is currently recommended.[64]

Transparent enrollment in AD clinical trials involving cognitively unimpaired research participants is generally believed to be safe and feasible[65] and is used in several trials of AD drugs involving cognitively unimpaired research participants.[66] It does require some safeguards to be put in place, notably, psychological screening and the provision of adequate counseling. The "how" of disclosure will be discussed in more detail below.

**To disclose or not to disclose?** Taken together, these three separately evolved bodies of literature on the ethics of disclosure of research results lead to the following general recommendations for AD prevention studies:

- In observational studies involving cognitively unimpaired research participants, AD biomarkers should not routinely be disclosed until clinical validity and utility can be established.

- Based on research participants' right to access their personal data, disclosure of AD biomarkers to individual participants should take place in research studies upon the explicit request of the individuals.

- When cognitively unimpaired participants are invited to take part in clinical trials, they should be informed about the reason they were selected. If selection took place based on AD biomarkers, this information should be disclosed—together with appropriate discussion of how it should be interpreted.

Hybrid studies in dementia prevention, such as the EPAD project in which observational and interventional research were combined, and clinical trials in which recruitment is based on preexisting biomarker data, are subject to all three sets of guidance. Based on these literatures, we advised against routine disclosure of AD biomarkers throughout the cohort study, while *allowing for*



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disclosure upon explicit request, and we even *demanded* disclosure upon recruitment for clinical trials, within one single—though hybrid—project. At first glance, the resulting overall disclosure policy for the EPAD project seems inconsistent and patchy. Yet it is perfectly in line with current ethical guidance. There are good reasons to withhold AD biomarker information as long as it is not strictly necessary to share it because, as said, this information is uncertain, not actionable, and difficult to interpret.

## RECOMMENDATIONS IN THE LITERATURE FOR AD BIOMARKER DISCLOSURE

As discussed, there are situations in which disclosure of AD biomarkers is unavoidable, either within ongoing observational studies, when participants explicitly ask for it, or as part of a transparent enrollment process for a clinical trial. If a research group decides to disclose AD biomarker test results to cognitively unimpaired research participants, they should do so responsibly. Current literature on AD biomarker disclosure puts forward the following four recommendations: First, because a research participant's decision to find out their test results should be well informed, researchers should educate participants about and discuss with them the clinical significance and limitations of AD biomarkers, the risks and benefits of learning AD biomarker information, and the lack of disease-modifying treatments at the outset of the clinical trial.[67] Studies have shown that cognitively unimpaired research participants may have difficulties understanding the uncertainties surrounding the clinical significance of AD biomarkers.[68] Biomarkers may easily be overinterpreted. It has been suggested that AD biomarker test results be given not in dichotomous forms (elevated versus nonelevated amyloid, for example, or amyloid positive or negative), but as numbers or percentages, in relation to a study threshold, to help participants interpret the results.[69] Research participants should receive written educational material, for which templates are available.[70] The researcher or study doctor should assess whether the research participant has understood relevant information about AD biomarkers, for instance, using the teach-back method. Research participants should receive correct and realistic information on currently available treatment or preventive options and should not be enticed with the promise of interventions that are still under clinical development.

Second, disclosure should take place during separate, face-to-face discussions with appropriately trained clinical experts (e.g., clinicians or counselors) who are skilled at effective communication and with sufficient time for questions.[71] Empirical studies suggest that research participants expect that the study doctor or researcher will take the time for discussion and interpretation of biomarker test results.[72] Third, it is recommended that some form of formal or informal psychological assessment should be conducted before disclosure of AD biomarker status[73] to ascertain whether the disclosure conversation may have potential adverse consequences for the research participant. Specifically, research participants who suffer from anxiety and depression may experience emotional difficulties after disclosure of AD biomarkers.[74] In these cases, disclosure may need to be postponed. At the same time, postponing disclosure may not help, and it may even exacerbate anxiety. Ideally, an assessment of individuals' psychological resilience to learn information about AD biomarkers should take place before enrollment. Fourth, it has been suggested that there should be some form of monitoring of the impact of disclosure,[75] for instance, through a follow-up telephone discussion, and that research participants and their families should be offered care and support if necessary.

While these recommendations seem to be aimed at promoting the safety of research participants and mitigating the risks associated with disclosure, we are concerned that some of these recommendations might have opposite effects. The offering of extensive information and high levels of care and support before and after disclosure may inadvertently reinforce overinterpretation of the clinical significance of AD biomarkers[76] and thus aggravate the psychological impact of AD biomarker disclosure. The special attention given to disclosure of AD biomarkers might reinforce an "exceptionalism" approach about AD biomarkers and enhance the special appeal and perceived utility of AD biomarkers.

To avoid this, it is important that due care and attention be given to the information provided and the process for doing so. Researchers should be very clear about what AD biomarkers can and cannot tell partici-



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pants about their future risk of developing AD dementia. In our view, the most important message about AD biomarkers is that they currently have limited predictive value and cannot answer the most common question of research participants in AD prevention studies, namely, whether they will or will not develop dementia in the future. In cognitively unimpaired individuals, this question cannot be answered by AD biomarkers alone. We suggest that this is the key message to be conveyed and reiterated during information provision, informed consent, and ongoing communication processes within AD research studies.

## CONCLUSION

In this article, we have explained the apparent conflicts within current ethics guidance for the disclosure of AD biomarkers to cognitively unimpaired research participants in prevention clinical trials by showing how norms for providing or withholding access to individual research results have developed within three separate literatures. Especially those who are setting up or evaluating hybrid research projects that combine a longitudinal cohort study with recruitment for clinical trials based on AD biomarkers will need to balance general arguments against routine disclosure to cognitively unimpaired research participants, given the limited clinical validity and clinical or personal utility of AD biomarkers, with arguments in favor of disclosure, given the individual's right to access personal research data and the ethical demands of transparent enrollment in clinical trials. This task lies ahead for a growing number of hybrid research projects and pre-recruitment efforts, including the Global Alzheimer's Platform, which is extending toward Europe.[77] Internationally, support for disclosure of AD biomarkers in research settings seems to be growing[78] and to be in line with both research participants' preferences and a broader societal trend to grant individuals more control over their personal data. Yet as long as AD biomarkers are not able to predict with a sufficient degree of certainty whether an individual will or will not develop AD dementia, their informational value is limited, and there are good reasons not to actively disclose them in research contexts. ♦

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## REFERENCES

1. Counts, S. E., et al., "Biomarkers for the Early Detection and Progression of Alzheimer's Disease," *Neurotherapeutics* 14, no. 1 (2017): 35-53.

2. Aisen, P., et al., "Registries and Cohorts to Accelerate Early Phase Alzheimer's Trials. A Report from the E.U./U.S. Clinical Trials in Alzheimer's Disease Task Force," *Journal of Prevention of Alzheimer's Disease* 3, no. 2 (2016): 68-74.

3. Sperling, R., et al., "Global Alzheimer's Platform Trial Ready Cohorts for the Prevention of Alzheimer's Dementia," *Journal of Prevention of Alzheimer's Disease* 3, no. 4 (2016): 185-87.

4. Solomon. A., et al., "European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): Study Protocol," *BMJ Open* 8, no. 12 (2019): e021017.

5. Ibid.

6. Rafii, M. S., and P. S. Aisen, "Alzheimer's Disease Clinical Trials: Moving toward Successful Prevention," *CNS Drugs* 33,



25782363, 2022, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/eahr.500146 by <Shibboleth>-member@gla.ac.uk, Wiley Online Library on [13/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

no. 2 (2019): 99-106.

7. Ritchie, C. W., et al., "Development of Interventions for the Secondary Prevention of Alzheimer's Dementia: The European Prevention of Alzheimer's Dementia (EPAD) Project," *Lancet Psychiatry* 3, no. 2 (2016): 179-86.

8. Langford, O., et al., "Predicting Amyloid Burden to Accelerate Recruitment of Secondary Prevention Clinical Trials," *Journal of Prevention of Alzheimer's Disease* 7, no. 4 (2020): 213-18.

9. Sperling, R. A., et al., "Toward Defining the Preclinical Stages of Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease," *Alzheimer's & Dementia* 7, no. 3 (2011): 280-92.

10. Jack, C. R., et al., "NIA-AA Research Framework: Toward a Biological Definition of Alzheimer's Disease," *Alzheimer's & Dementia* 14, no. 4 (2018): 535-62.

11. Dubois, B., et al., "Clinical Diagnosis of Alzheimer's Disease: Recommendations of the International Working Group," *Lancet Neurology* 20, no. 6 (2021): 484-96, at 484.

12. Brookmeyer, R., and N. Abdalla, "Estimation of Lifetime Risks of Alzheimer's Disease Dementia Using Biomarkers for Preclinical Disease," *Alzheimer's & Dementia* 14, no. 8 (2018): 981-88.

13. Altomare, D., et al., "Prognostic Value of Alzheimer's Biomarkers in Mild Cognitive Impairment: The Effect of Age at Onset," *Journal of Neurology* 266 (2019): 2535-45.

14. Roberts, R. O., et al., "Prevalence and Outcomes of Amyloid Positivity among Persons without Dementia in a Longitudinal, Population-Based Setting," *JAMA Neurology* 75, no. 8 (2018): 970-79; Altomare et al., "Prognostic Value of Alzheimer's Biomarkers in Mild Cognitive Impairment."

15. Petersen, R. C., et al., "Practice Guideline Update Summary: Mild Cognitive Impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology," *Neurology* 90, no. 3 (2018): 126-35.

16. Grill, J. D., et al., "Disclosure of Amyloid Status Is Not a Barrier to Recruitment in Preclinical Alzheimer's Disease Clinical Trials," *Neurobiology of Aging* 39 (2016): 147-53.

17. Largent, E. A., et al., "Cognitively Unimpaired Adults' Reactions to Disclosure of Amyloid PET Scan Results," *PLoS One* 15, no. 2 (2020): e0229137.

18. Milne, R., et al., "Perspectives on Communicating Biomarker-Based Assessments of Alzheimer's Disease to Cognitively Healthy Individuals," *Journal of Alzheimer's Disease* 62, no. 2 (2018): 487-98; Vanderschaeghe, G., et al., "Amnestic MCI Patients' Experiences after Disclosure of Their Amyloid PET Result in a Research Context," *Alzheimer's Research & Therapy* 9, no. 1 (2017): 92.

19. Largent et al., "Cognitively Unimpaired Adults' Reactions."

20. Caselli, R. J., et al., "Public Perceptions of Presymptomatic Testing for Alzheimer Disease," *Mayo Clinic Proceedings* 89, no. 10 (2014): 1389-96; Ott, B. R., et al., "A Survey of Knowledge and Views Concerning Genetic and Amyloid Positron Emission Tomography Status Disclosure," *Alzheimer's & Dementia* 2, no. 1 (2016): 23-29.

21. Declaration of Helsinki, World Medical Association, October 2000, https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

22. National Academies of Sciences, Engineering, and Medicine, *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm*, ed. Downey, A. S., et al. (Washington, DC: National Academies Press, 2018), https://nap.nationalacademies.org/catalog/25094/returning-individual-research-results-to-participants-guidance-for-a-new, p. xxv.

23. Bredenoord, A. L. et al., "Disclosure of Individual Genetic Data to Research Participants: The Debate Reconsidered," *Trends in Genetics* 27, no. 2 (2011): 41-47.

24. Wolf, S. M., "Return of Individual Research Results and Incidental Findings: Facing the Challenges of Translational Science," *Annual Review of Genomics and Human Genetics* 14 (2013): 557-77; De Clercq, E., et al., "Returning Results in Biobank Research: Global Trends and Solutions," *Genetic Testing and Molecular Biomarkers* 21, no. 3 (2017): 128-31.

25. Thorogood, A., G. Dalpé, and B. M. Knoppers, "Return of Individual Genomic Research Results: Are Laws and Policies Keeping Step?," *European Journal of Human Genetics* 27, no. 4 (2019): 535-46, at 535.

26. Knoppers, B. M., M. H. Zawati, and K. Sénécal, "Return of Genetic Testing Results in the Era of Whole-Genome Sequencing," *Nature Reviews Genetics* 16, no. 9 (2015): 553-59.

27. Lewczuk, P., et al., "Cerebrospinal Fluid and Blood Biomarkers for Neurodegenerative Dementias: An Update of the Consensus of the Task Force on Biological Markers in Psychiatry of the World Federation of Societies of Biological Psychiatry," *World Journal of Biological Psychiatry*?19, no. 4 (2018): 244-328, at 277.

28. Smedinga, M., et al., "The Framing of 'Alzheimer's Disease': Differences between Scientific and Lay Literature and Their Ethical Implications," *Gerontologist* 61, no. 5 (2020): 746-55.

29. Lingler, J. H., and W. E. Klunk, "Disclosure of Amyloid Imaging Results to Research Participants: Has the Time Come?," *Alzheimer's & Dementia* 9, no. 6 (2013): 741-44.

30. Bemelmans, S. A., et al., "Psychological, Behavioral and Social Effects of Disclosing Alzheimer's Disease Biomarkers to Research Participants: A Systematic Review," *Alzheimer's Research & Therapy* 8, no. 1 (2016): doi:10.1186/s13195-016-0212-z; De Wilde, A., et al., "Disclosure of Amyloid Positron Emission Tomography Results to Individuals without De-



25782363, 2022, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/eahr.500146 by <Shibboleth>-member@gla.ac.uk, Wiley Online Library on [13/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

mentia: A Systematic Review," *Alzheimer's Research & Therapy* 10, no. 1 (2018): doi:10.1186/s13195-018-0398-3; Kim, H., and J. H. Lingler, "Disclosure of Amyloid PET Scan Results: A Systematic Review," *Progress in Molecular Biology and Translational Science* 165 (2019): 401-14.

31. Erickson, C. M., et al., "Disclosure of Preclinical Alzheimer's Disease Biomarker Results in Research and Clinical Settings: Why, How, and What We Still Need to Know," *Alzheimer's & Dementia* 13, no. 1 (2021): doi:10.1002/dad2.12150.

32. Largent et al., "Cognitively Unimpaired Adults' Reactions."

33. Milne, R., et al., "At, with and beyond Risk: Expectations of Living with the Possibility of Future Dementia," *Sociology of Health & Illness* 40, no. 6 (2018): 969-87.

34. Lewczuk et al., "Cerebrospinal Fluid and Blood Biomarkers."

35. Lineweaver, T. T., et al., "Effect of Knowledge of APOE Genotype on Subjective and Objective Memory Performance in Healthy Older Adults," *American Journal of Psychiatry* 171, no. 2 (2014): 201-8.

36. Erickson et al., "Disclosure of Preclinical Alzheimer's Disease Biomarker Results."

37. Bunnik, E. M., et al., "On the Personal Utility of Alzheimer's Disease-Related Biomarker Testing in the Research Context," *Journal of Medical Ethics* 44, no. 12 (2018): 830-34.

38. Brookmeyer and Abdalla, "Estimation of Lifetime Risks of Alzheimer's Disease Dementia."

39. Bunnik et al., "On the Personal Utility of Alzheimer's Disease-Related Biomarker Testing."

40. Gooblar, J., et al., "Attitudes of Research Participants and the General Public regarding Disclosure of Alzheimer Disease Research Results," *JAMA Neurology* 72, no. 12 (2015): 1484-90.

41. Largent et al., "Cognitively Unimpaired Adults' Reactions."

42. Beauchamp, T. L., and J. F. Childress, *Principles of Biomedical Ethics*, 6th ed. (New York: Oxford University Press, 2008).

43. Schickhardt, C., H. Fleischer, and E. C. Winkler, "Do Patients and Research Subjects Have a Right to Receive Their Genomic Raw Data? An Ethical and Legal Analysis," *BMC Medical Ethics* 21, no. 1 (2020): doi:10.1186/s12910-020-0446-y.

44. Council of Europe, "Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine," ETS No. 164., article 10.2, 1997, https://www.coe.int/en/web/conventions/full-list?module=treaty-detail&treatynum=164.

45. General Data Protection Regulation (GDPR), European Union, 2018, https://gdpr.eu/.

46. Thorogood, A., et al., "APPLaUD: Access for Patients and Participants to Individual Level Uninterpreted Genomic Data," *Human Genomics* 12, no. 1 (2018): doi:10.1186/s40246-018-0139-5.

47. Schickhardt, Fleischer, and Winkler, "Do Patients and Research Subjects Have a Right to Receive Their Genomic Raw Data?"

48. National Academies of Sciences, Engineering, and Medicine, *Returning Individual Research Results to Participants*.

49. Nebeker, C., A. D. Leow, and R. C. Moore, "From Return of Information to Return of Value: Ethical Considerations When Sharing Individual-Level Research Data," *Journal of Alzheimer's Disease* 71, no. 4 (2019): 1081-88.

50. Mattos, M. K., and J. H. Lingler, "Research Data Disclosure in the Digital Age," *Journal of Alzheimer's Disease* 71, no. 4 (2019): 1089-91.

51. Erickson et al., "Disclosure of Preclinical Alzheimer's Disease Biomarker Results."

52. Lewis, A. C. F., B. M. Knoppers, and R. C. Green, "An International Policy on Returning Genomic Research Results," *Genome Medicine* 13, no. 1 (2021): 115.

53. Budin-Ljøsne, I., et al., "Feedback of Individual Genetic Results to Research Participants: Is It Feasible in Europe?," *Biopreservation and Biobanking* 14, no. 3 (2016): 241-48.

54. National Academies of Sciences, Engineering, and Medicine, *Returning Individual Research Results to Participants*, 73-74.

55. Milne et al., "Perspectives on Communicating Biomarker-Based Assessments."

56. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington, DC: U.S. Government Printing Office, 1979).

57. Ibid., 5.

58. Ibid., 11.

59. Council for International Organisations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-Related Research Involving Humans* (Geneva: CIOMS, 2016).

60. Lewczuk et al., "Cerebrospinal Fluid and Blood Biomarkers."

61. Roberts, J. S., L. B. Dunn, and G. D. Rabinovici, "Amyloid Imaging, Risk Disclosure and Alzheimer's Disease: Ethical and Practical Issues," *Neurodegenerative Disease Management* 3, no. 3 (2013): 219-29.

62. Kim, S. Y. H., J. Karlawish, and B. E. Berkman, "Ethics of Genetic and Biomarker Test Disclosures in Neurodegenerative Disease Prevention Trials," *Neurology* 84, no. 14 (2015): 1488-94.

63. Molinuevo, J. L., et al., "Ethical Challenges in Preclinical Alzheimer's Disease Observational Studies and Trials: Results of the Barcelona Summit," *Alzheimer's & Dementia* 12, no. 5



25782363, 2022, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/eah.50046 by <Shibboleth>-member@gla.ac.uk, Wiley Online Library on [13/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(2016): 614-22, at 619.

64. Ibid.

65. Ibid.

66. Harkins, K., et al., "Development of a Process to Disclose Amyloid Imaging Results to Cognitively Normal Older Adult Research Participants," *Alzheimer's Research & Therapy* 7, no. 1 (2015): 26; Langlois, C. M., et al., "Alzheimer's Prevention Initiative Generation Program: Development of an APOE Genetic Counseling and Disclosure Process in the Context of Clinical Trials," *Alzheimer's & Dementia* 5 (2019): 705-16; Grill, J. D., et al., "Short-Term Psychological Outcomes of Disclosing Amyloid Imaging Results to Research Participants Who Do Not Have Cognitive Impairment," *JAMA Neurology* 77, no. 12 (2020): 1504-13.

67. Vanderschaeghe, G., et al., "From Information to Follow-up: Ethical Recommendations to Facilitate the Disclosure of Amyloid PET Scan Results in a Research Setting," *Alzheimer's & Dementia* 4 (2018): 243-51.

68. Mozersky, J., et al., "Comprehension of an Elevated Amyloid Positron Emission Tomography Biomarker Result by Cognitively Normal Older Adults," *JAMA Neurology* 75, no. 1 (2018): 44-50; Rostamzadeh, A., et al., "Health Literacy in Individuals at Risk for Alzheimer's Dementia: A Systematic Review," *Journal of Prevention of Alzheimer's Disease* 7, no. 1 (2020): 47-55.

69. Mozersky et al., "Comprehension of an Elevated Amyloid Positron Emission Tomography Biomarker."

70. Harkins et al., "Development of a Process to Disclose Amyloid Imaging Results."

71. Ibid.

72. Milne et al., "Perspectives on Communicating Biomarker-Based Assessments."

73. Harkins et al., "Development of a Process to Disclose Amyloid Imaging Results."

74. Green, R. C., et al., "Disclosure of APOE Genotype for Risk of Alzheimer's Disease," *New England Journal of Medicine* 361, no. 3 (2009): 245-54.

75. Harkins et al., "Development of a Process to Disclose Amyloid Imaging Results."

76. Milne et al., "Perspectives on Communicating Biomarker-Based Assessments."

77. Dwyer, J., et al., "Global Alzheimer's Platform Foundation™ (GAP) Development of a Transatlantic Alzheimer's Disease Clinical Trial Network," *Alzheimer's & Dementia* 17, no. S9 (2021): doi:10.1002/alz.052297.

78. Erickson et al., "Disclosure of Preclinical Alzheimer's Disease Biomarker Results."



25782363, 2022, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/eahr.500146 by <Shibboleth>-member@gla.ac.uk, Wiley Online Library on [13/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License