HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

J Alzheimers Dis. 2022 ; 90(3): 1035–1043. doi:10.3233/JAD-220113.

Spillover: The Approval of New Medications for Alzheimer's Disease Dementia Will Impact Biomarker Disclosure Among Asymptomatic Research Participants

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Abstract

In this article we address how the recent, and anticipated upcoming, FDA approvals of novel anti-amyloid medications to treat individuals with mild Alzheimer's disease (AD) dementia could impact disclosure of biomarker results among asymptomatic research participants. Currently, research is typically the context where an asymptomatic individual may have the option to learn their amyloid biomarker status. Asymptomatic research participants who learn their amyloid status may have questions regarding the meaning of this result and the implications for accessing a potential intervention. After outlining our rationale, we provide examples of how current educational materials used in research convey messages regarding amyloid positivity and the

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Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/22-0113r1).

availability of treatments, or lack thereof. We suggest language to improve messaging, as well as strengths of current materials, in addressing these issues for research participants. Although novel medications are currently only approved for use among symptomatic individuals, their availability may have implications for disclosure among asymptomatic research participants with evidence of amyloid deposition, who may be especially interested in information on these interventions for potential prevention, or future treatment, of mild cognitive impairment or dementia due to AD.

Keywords

Alzheimer's disease; amyloid; asymptomatic disclosure; biomarkers; dementia; new medications; research ethics

In June 2021, the FDA granted accelerated approved for the anti-amyloid monoclonal antibody aducanumab (trade name Aduhelm©) for the treatment of Alzheimer's disease (AD) [1]. Although initially approved for broad use in the treatment of "Alzheimer's disease," the approval was rapidly narrowed for use in those with "mild cognitive impairment or mild dementia" to more accurately reflect the initial clinical trial participants [2–5]. Similar drugs are in the pipeline, including several that have been granted special FDA fast track designation [6], and may also be granted accelerated approval. Given the relatively slow progress in the development of medications for AD dementia to date, the approval of a new medication generated a great deal of excitement, as well as controversy [2–4, 7].

A major source of controversy was the accelerated approval pathway, which allows use of surrogate endpoints [3, 4]. Using surrogate endpoints speeds up approval for "serious conditions" lacking current interventions, and where the surrogate endpoint is "reasonably likely" to predict clinical benefit [8]. AD is a serious disease—affecting more than 6 million Americans currently—for which there have been no disease modifying therapies, providing part of the rationale for the accelerated approval pathway [9]. However, marketing approval for aducanumab was granted based on the surrogate endpoint of a reduction in amyloid-beta plaques rather than the clinical endpoint of improved cognitive functioning. That is, the drug was approved based on its ability to reduce amyloid plaque, not to stabilize or slow cognitive decline.

Although the presence of amyloid plaques is required for a pathological diagnosis of AD, it has not been established that a reduction in amyloid slows or stabilizes the clinical signs and symptoms of AD [3, 4, 10–14]. Evidence to date suggests little, if any, clinical benefit from amyloid reduction [10–14]. The FDA gave Biogen, the maker of aducanumab, until 2030 to provide new data regarding clinical outcomes. Aducanumab also carries substantial risks including brain swelling and bleeding, creating an unacceptable riskbenefit ratio for many given the lack of evidence of clinical benefit [4, 5, 10]. Recently, the Center for Medicare and Medicaid Services (CMS) issued a final ruling that aducanumab, and similar anti-amyloid agents that receive FDA approval on the basis of surrogate endpoint changes rather than clinical efficacy, will only be covered by Medicare in the context of randomized clinical trials. If there is evidence of clinical benefit for a drug, coverage will broaden [10].

AMYLOID AS SURROGATE ENDPOINT: POTENTIAL FOR MISUNDERSTANDING

The approval of medications based on the surrogate endpoint of amyloid reduction could lead to confusion or misunderstanding by the public, non-specialist clinicians, and even some specialist clinicians. Based on the surrogate endpoint, it might seem logical to assume that a reduction in amyloid slows cognitive decline and therefore that an effective treatment for AD is now available. In fact, FDA statements use language—necessary for the accelerated approval pathway—that suggests this connection, stating that amyloid reduction "is reasonably likely to predict important benefits to patients" [15]. The approval of aducanumab received a great deal of media attention, including from patient organizations who promoted the news, often using the FDA language about the "reasonable likelihood" that reducing amyloid leads to clinical benefits [16]. In light of the current approval and media attention, there may be a broader public misperception that AD dementia is now treatable by reducing amyloid, despite the current evidence suggesting otherwise.

IMPACT ON ASYMPTOMATIC BIOMARKER DISCLOSURE

Currently, research participation is typically how an asymptomatic individual may learn their biomarker amyloid status, as clinical guidelines do not recommend amyloid testing among asymptomatic individuals [17]. An increasing number of asymptomatic AD research participants are learning their amyloid status as part of research [18]. In some cases, amyloid results are disclosed because they determine clinical trial eligibility (or exclusion), in other cases they are disclosed to interested participants in longitudinal cohorts, and in some settings they are returned in research studies specifically designed to assess the impact of disclosure [18–25]. In a recent survey of Alzheimer Disease Research Centers (ADRCs) regarding disclosure among their longitudinal cohorts, approximately a quarter of centers indicated amyloid results are disclosed to some asymptomatic individuals, although the data do not indicate the specific studies or contexts in which these results were offered [18]. Many asymptomatic AD research participants have a family history of AD, may be experiencing subjective memory concerns [26], and are aware of AD research and new advances, in addition to being most likely to access biomarker results such as amyloid positivity.

Ongoing approvals and increasing awareness of novel medications could impact disclosure of amyloid status to asymptomatic research participants, even though aducanumab is currently only approved for symptomatic individuals. Research studies that involve biomarker disclosure incorporate educational materials to provide participants with information prior to learning their biomarker results.[1] Two ethical concerns regarding asymptomatic disclosure of amyloid status that are described in educational materials used in research are the lack of available treatments and the limited predictive value of amyloid positivity. Below we provide examples of how current research materials convey these

[1]These educational materials are distinct from informed consent documents, and provide supplemental information specifically regarding biomarkers and disclosure of biomarker status.

messages, with suggestions for what key messages should continue, and what additions may be needed, especially as novel medications are approved or new evidence emerges.

DESCRIPTIONS OF TREATMENT AVAILABILITY

A major concern regarding disclosure of amyloid status (and other AD biomarker risk information) has been the lack of available treatments to date [17, 27–29]. This information is thought to lack clinical utility, and clinical guidelines do not recommend disclosure [17, 30–33]. The potential psychological harms of knowing that one is facing a highly feared disease, for which there are no treatments, has dominated concerns regarding the harms of disclosure for asymptomatic individuals [28, 34, 35]. Most research disclosure materials emphasize this information, but each uses slightly different language (Table 1).

If some individuals perceive that AD is now treatable, materials may need to include additional information about evidence regarding current medications, or lack thereof. Individuals who are amyloid positive may have questions about treatments, or desire information about accessing medications. Materials will need to convey accurate information about what is currently known about medications, and the populations in whom they are approved, while also being flexible and changing as new evidence emerges. We suggest that researchers avoid using overly broad language such as “treatments” which can include non-pharmacological interventions. When describing pharmacological interventions, researchers should refer to “medications” aimed at improving cognition when describing anti-amyloid drugs, to distinguish these medications from those that alleviate some of the symptoms of AD dementia (i.e., agitation) but are not aimed at cognition (Table 2).

DESCRIPTIONS OF AMYLOID POSITIVITY: EMPHASIZING LIMITED PREDICTIVE VALUE

Among asymptomatic individuals, the presence of amyloid does not necessarily mean one will go on to develop AD dementia. In fact, many individuals with elevated amyloid will not go on to develop AD dementia in their lifetime [39–43], which is an argument against asymptomatic disclosure [17].

Materials to date emphasize the unclear relationship between amyloid positivity and developing AD dementia (Table 3), highlighting the possibility of having elevated amyloid and never developing AD dementia. Research participants who received “elevated” amyloid results in the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) study understood the uncertainty of this result and that it did not indicate they would definitely develop AD dementia, although a small portion perceived amyloid positivity to mean AD dementia was imminent [21]. Messaging that emphasizes this uncertainty should continue going forward. Notably, participants who received “not elevated” amyloid results expressed substantial relief and joy, even being “ecstatic,” suggesting they may not be attuned to the converse possibility that they could still develop AD dementia in future [22]. Materials should further emphasize that being amyloid negative now could change in future (Table 4).

Asymptomatic research participants who learn their amyloid status may have questions about aducanumab's suitability should they develop symptoms. They may even inquire about off label use to reduce amyloid burden as a means of prevention—especially if they already have subjective memory concerns. Given the potential for misunderstanding that amyloid positivity means they *will* get dementia, and that aducanumab can slow or prevent cognitive decline by reducing amyloid, research participants may be especially interested in learning more about it. Additional information may need to be added indicating that a reduction in amyloid does not necessarily slow the development or progression of symptoms, should they develop in the future (Table 4). There are ongoing clinical trials of other anti-amyloid antibodies for prevention in amyloid positive asymptomatic individuals [20, 45], reflecting the current lack of knowledge about these strategies, while also suggesting a future direction where medications may target asymptomatic individuals.

DISCUSSION

Asymptomatic research participants—who often have family histories of AD and/or subjective memory concerns, and are currently the group most likely to learn their amyloid status as part of research—may have questions about the recent and possible upcoming approval(s) of novel anti-amyloid medications for mild cognitive impairment and mild dementia due to AD. However, current medications are only approved for use in symptomatic individuals, and even among this population there is limited evidence of clinical benefit, and the potential harms are substantial. Therapies aimed at individuals in the pre-symptomatic stage remain a hopeful future direction given the belief that early intervention may be most effective, before the pathophysiological process is too advanced [30]. However, no medications are currently approved for prevention of cognitive decline in individuals without symptoms, nor is there evidence to support such use. In light of this, biomarker disclosure may need to include additional information that there is no evidence to support use of medications among asymptomatic individuals currently, while also clearly conveying the unclear relationship between amyloid positivity and cognitive symptoms.

Evidence is changing quickly as new data emerges, and messaging will need to adapt and change as the evidence base changes. Materials may require more nuanced messaging regarding medications and the populations in whom they are approved, and we have provided language for others to use and adapt. If new data reveal actual benefits of anti-amyloid or other therapies going forward, disclosure information would need to be updated accordingly.

Messaging regarding amyloid positivity will also need to adapt as data emerges. When additional biomarker data, such as MRI findings or tau status, are combined with amyloid findings, the predictive value appears to improve compared to amyloid on its own [47, 48]. However, research participants are unlikely to receive such comprehensive results, either because other markers have not been evaluated, or because of limited consensus on how to interpret these findings beyond qualitative statements, given current limitations. At present, we are only aware of one study taking this approach by disclosing the estimated absolute 5 year risk of AD dementia based on three combined results: PET amyloid, MRI hippocampal volume, and *APOE* status [23]. In addition, information that enables amyloid disclosure

to move beyond the current binary of “elevated” or “not elevated” may be highly desired by participants, who may want to know how “elevated” their amyloid is, or what this result means for their personal risk of developing AD dementia [21, 24]. Ongoing research is evaluating how additional factors, such as amyloid burden, other imaging findings, or demographics, can improve the predictive value of a positive amyloid test [39, 49, 50] and this information may be incorporated in disclosure processes in future.

Therefore, as new biomarker data is incorporated into prediction models for whether and when individuals are expected to progress, messages about uncertainty will need to adapt again to reflect the evidence base. For now, when describing the limited predictive value of amyloid positivity, materials may need to add information – based on the limited information currently available – that reducing amyloid does not appear to slow or halt the progression of clinical signs and symptoms. This may be of particular interest to asymptomatic research participants curious about whether they could be eligible for novel anti-amyloid therapies.

Data and evidence may also change as we increase the diversity and representativeness of AD research participants, who at present are predominantly white and educated, limiting the generalizability of AD research [51–53]. Overall, AD research is plagued by a lack of representation, including most studies of amyloid positivity cited above, as well as the aducanumab trials, in which only 19 participants (0.06%) self-identified as Black [54]. Moreover, the data we have on individuals’ desire to know their biomarker status also comes from predominantly white and educated populations [55–57], further emphasizing our ethical obligation to increase diversity in the AD research enterprise.

Maintaining trust and confidence in AD research, science, and medicine may be especially important currently, when many novel medications are receiving attention and approvals. Public trust could be reduced if FDA processes are viewed with suspicion or seen to be biased, or if there is changing messaging regarding evidence, or lack thereof, about medications. As has been evidenced during the COVID-19 pandemic, when public trust in government agencies and science is diminished, uptake of interventions may be low and public health can suffer as a result [58, 59]. Communicating honestly and transparently with participants about what we do and do not know is therefore essential. Ultimately, disclosure of AD biomarkers will likely increase as new medications are approved and new data become available, and our messaging will need to evolve with emerging evidence.

ACKNOWLEDGMENTS

This paper was written by members of the Asymptomatic Subcommittee and Data/Analytics Subcommittee on behalf of the national Advisory Group on Risk Evidence Education for Dementia (AGREED). AGREED is led by Neelum T. Aggarwal, MD (Rush University Medical Center), Allyson Rosen, PhD (Stanford School of Medicine and Palo Alto VA Healthcare System), and Carey Gleason, PhD (University of Wisconsin School of Medicine and Public Health). For more information on the activities of AGREED and a full listing of its membership (including researchers, clinicians, educators, advocates, and community members), see http://www.agreedementia.org. The authors thank AGREED committee members for permission to use text from research materials and/or feedback on initial drafts of the paper: Jason Karlawish, MD (University of Pennsylvania), Robert Green, MD (Brigham and Women’s Hospital) and Jessica Langbaum, PhD (Banner Alzheimer’s Institute), and Rebecca Ferber (University of Michigan).

This research was supported by National Institute on Aging (NIA) grants R01AG065234 (to JM), P30AG053760 (to JSR), P30AG062421 (to DB and P30AG066509 (to EMW)). Dr. Mozersky has also received support from National Institutes of Health (NIH) grants P30 AG066444, P01AG026276, P01AG03991, and UL1TR002345. Dr. Roberts has research support (including paid travel to national meetings) from NIH grants R01AG0588468, R01 AG062528, R01AG058724, R01HG010679,U01CA232827, R03AG063222, and R21AG066644, as well as American Cancer Society grant RSG-20-025 and the University of Michigan Depression Center. Dr. Blacker has additional support from NIH grants 1P30AG073107, 1R01AG073410, 1U01AG068221, 1U01AG076478, 2P01AG032952, 3R01AG062282, 5U01AG032984, 5P01AG036694, 5R01AG058063, 5R01AG062282, 5R01AG063975, 5R01AG066793, and 5U24NS100591, as well as from the president and fellows of Harvard College. Ms. Rumbaugh has received support from research grants funded by the NIA and the Parkinson's Foundation. Dr. Wijsman has additional support from NIH grants R01 AG059737, U01 AG052409, U01 AG058589, R01 HD088431, and the Metropolitan Life Foundation. Dr. Galasko has received research support from NIH grant P30AG062429 and The State of California. Dr. Chhatwal has support from NIH grants P01AG036694, R01 AG062667, R01 AG071865, and the Doris Duke Charitable Foundation. Ms. Rumbaugh and Dr. Galasko have also received research support from the Michael J. Fox Foundation.

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Table 1

Sample descriptions of lack of treatments in current research educational materials

"There is currently no cure or prevention for AD dementia. There are only treatments to help some of the symptoms" (educational brochure) "There are currently no proven ways to prevent or cure AD dementia" (questions to consider) Washington University Study of Having AD dementia Research results Explained (WeSHARE) [23, 24]
"Although much is known about the disease's biology, and treatments are available for some of its symptoms, there is currently no cure or prevention for Alzheimer's disease." (educational brochure) "There are no proven ways to prevent Alzheimer's disease from developing" (questions to consider) Risk Evaluation and Education for Alzheimer's Disease (REVEAL II) [36, 37]
"Although we are learning more about the cause of the disease, and treatments are available for some of its symptoms, there is currently no cure or prevention for Alzheimer's disease." (educational brochure) Risk Evaluation and Education for Alzheimer's Disease (REVEAL III) [37, 38]

Table 2

Suggested language regarding lack of treatments[a]

Emphasize what is currently known based on evidence: – “There are no cures for AD dementia” – “There is no proven way to prevent AD dementia” – “Leading a healthier lifestyle may help reduce your risk of developing AD dementia”
Address the limited evidence regarding currently approved anti-amyloid medication(s) by including a statement such as: – “A newly approved medication is available, but the evidence that it helps with memory or thinking is limited”, or – “There is limited evidence that the newly approved medication will help with memory and thinking problems” or – “The newly approved medication may help reduce amyloid, but it is not yet clear if this will help with memory and thinking problems”
Address the limited population for whom anti-amyloid medications are currently approved and limited coverage using statements such as[b]: – “The currently approved medication is only for individuals diagnosed with mild memory and thinking problems caused by AD dementia” – “The currently approved medication is only covered by Medicare in a clinical trial, and only for patients with evidence that memory and thinking problems are caused by underlying Alzheimer’s disease” – “There are also clinical trials studying whether giving medication to people with no memory or thinking problems can prevent them from developing these problems in the future. There are no medications approved for this use currently.”

[a]This language can be used verbatim or adapted based on specific needs and contexts. Throughout we use the singular. As additional medications are approved, language should be updated to indicate there is more than one approved drug.

[b]This language may need to be updated as new medications, evidence, or coverage decisions emerge.

Table 3

Sample description of amyloid positivity in current research educational materials

"Every person with AD dementia has a buildup of 2 proteins in their brain, called amyloid and tau. These proteins build up in the brain over many years before they cause any memory and thinking problems. Not everyone who has this buildup will develop AD dementia. AD researchers want to better understand why some people with buildup of these proteins develop AD dementia, while others don't. Researchers have learned that: • Not all people who show these AD biomarkers will develop AD dementia. Some people with AD biomarkers will never get memory and thinking problems. • Some people who do not have any of these AD biomarkers now may still develop memory and thinking problems later." Washington University Study of Having AD dementia Research results Explained (WeSHARE) [23, 24]
"Though research studies so far suggest older individuals with evidence of amyloid buildup may be at higher risk for memory loss, this does not mean every person with elevated amyloid buildup will develop the clinical symptoms of AD. In fact, an important part of the A4 study is to learn more about brain markers and other tests to help doctors predict who will experience memory decline and progress towards AD dementia." Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4 study) [20, 44]
"Recent research studies suggest that people over the age of 65 who have evidence of higher than normal levels of amyloid plaques in their brains are at higher risk for dementia due to Alzheimer's disease. However, not every person who has higher than normal levels of amyloid plaques will develop dementia due to Alzheimer's disease." "It is important to remember that elevated levels of amyloid plaques do not necessarily mean a person will develop dementia due to Alzheimer's disease. Some studies suggest that about 30 percent of older people with normal memory and thinking abilities also have elevated levels of amyloid plaques in their brains." Alzheimer's Prevention Initiative Generation Program [45]
"Recent research studies suggest older people with evidence of amyloid plaques are at higher risk for memory loss compared to older people without evidence of amyloid plaques. This does not mean every person with elevated amyloid will develop the clinical symptoms of Alzheimer's disease dementia." "Studies suggest elevated levels of amyloid in the brain increase the risk of developing Alzheimer's disease dementia and that this risk is spread out over years or even decades. Some people with elevated levels of amyloid in their brain may never develop dementia in their lifetime." Impact of Disclosing Amyloid Imaging Results to Cognitively Normal Individuals (REVEAL-SCAN) [46]

Table 4

Suggested language regarding amyloid positivity[c]

Continue to emphasize what is currently known:
– A person with a positive[d] amyloid result has a higher risk of developing AD dementia, but it does not mean they will definitely develop AD dementia within their lifetime. – A positive amyloid result by itself cannot predict whether someone will definitely develop memory or thinking problems caused by AD dementia or when this may happen. – Amyloid is necessary but not sufficient for the development of AD dementia – There are other causes of dementia besides Alzheimer's disease. Amyloid results cannot tell you about these other causes, only about dementia caused by AD.
Consider adding a statement that medications to reduce amyloid have not been shown to slow or stabilize cognitive decline: – New medications can help reduce amyloid in the brain, but it is still unknown if reducing amyloid will help with memory and thinking problems.
Consider adding a statement that being amyloid *negative* now does not guarantee one will not develop AD in future given evidence suggesting this message is not always well understood: – Your amyloid result is a "snapshot" of your brain at a certain time. Being amyloid negative now could change in future.

[c] This language can be used verbatim or adapted based on specific needs and contexts.

[d] We use the word positive here to indicate a result of "elevated" amyloid. Researchers should use the term most suitable for their context, and most studies currently refer to "elevated".