Ethical challenges in preclinical Alzheimer's disease observational studies and trials: Results of the Barcelona summit

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Abstract

Alzheimer’s disease (AD) is among the most significant health care burdens. Disappointing results from clinical trials in late-stage AD persons combined with hopeful results from trials in persons with early-stage suggest that research in the preclinical stage of AD is necessary to define an optimal therapeutic success window. We review the justification for conducting trials in the preclinical stage and highlight novel ethical challenges that arise and are related to determining appropriate risk-benefit ratios and disclosing individuals’ biomarker status. We propose that to conduct clinical trials with these participants, we need to improve public understanding of AD using unified vocabulary, resolve the acceptable risk-benefit ratio in asymptomatic participants, and disclose or not biomarker status with attention to study type (observational studies vs clinical trials). Overcoming these challenges will justify clinical trials in preclinical AD at the societal level and aid to the development of societal and legal support for trial participants.

Keywords: Alzheimer’s disease; Preclinical AD; Ethics; Asymptomatic
1. Introduction

By the year 2030, 76 million people worldwide will suffer from dementia, with most cases being caused by Alzheimer’s disease (AD) [1]. Despite the considerable advances in our understanding of the neuropathologic processes that underpin AD, academic and industry research programs that develop mechanism-based therapies, including those directed against β-amyloid have yet to produce meaningful clinical benefits [2]. Consequently, one of the biggest questions that the AD research community faces is whether clinical trials have so far included participants who have already surpassed the optimal therapeutic window for intervention, together with the need to ensure the presence of AD pathology through biomarkers.

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINDS-ADRDA, now the Alzheimer’s Association) published for the first time the clinical diagnostic criteria for AD [3]. Almost 30 years later, the progress in our scientific understanding of the neuropathology that precedes clinical symptoms prompted the scientific community to redefine AD as a pathologic continuum. Both the International Working Group and the US National Institute of Aging with the Alzheimer’s Association (NIA-AA) released revised guidelines that incorporated biomarkers to identify individuals at risk of developing AD dementia [4–8]. Both criteria subdivide AD development into three stages: preclinical (abnormal biomarkers and no or only subtle cognitive impairment), mild cognitive impairment (MCI) due to AD or prodromal AD (defined as the presence of abnormal pathophysiological biomarkers and episodic memory impairment) and dementia (abnormal biomarkers and clear cognitive and functional impairment).

One significant advance in our understanding of AD is that it has two components: a neuropathologic one, which remains asymptomatic during years, and a clinical one, which starts with a MCI stage followed by a dementia one. Convergent biomarker and imaging findings from autosomal dominant AD mutation carriers, genetic at-risk and age at-risk cohorts suggest that the pathophysiological process of AD starts over a decade before the dementia stage [9–14]. This asymptomatic phase, referred to as preclinical AD, has given us an unprecedented opportunity to perform observational studies and trials to intervene at earlier stages of the continuum and delay the onset of clinical decline and ultimately dementia. In this scenario, trials in mild moderate AD have been consistently negative during the last decade [15], and although we are still waiting for the results of ongoing prodromal AD trials, intervention studies on asymptomatic individuals appear as highly relevant and promising, before substantial irreversible neuronal network dysfunction and loss, associated with overt clinical symptoms, have occurred.

Conducting preclinical AD trials gives rise to a variety of novel ethical and policy challenges. These include whether to disclose genetic and/or biomarker results to an individual, the need to determine an acceptable risk-benefit ratio in asymptomatic participants and the legal protection of participants from insurance policies. The ethical framework that guides clinical research can be seen as a balancing among the interests of the participants and society on one side, as well as the research challenges on the other [16]. To review and discuss the novel ethical challenges that need to be overcome for successful performance of trials in the preclinical stage of AD, a multistakeholder group met in a 1-day summit entitled “Ethical challenges of future Alzheimer’s disease clinical research” held in Barcelona in October 2014. This reunion was organized by the Barcelona-βeta Brain Research Center, the research institute where the Pasqual Maragall Foundation conducts all its scientific activities devoted to clinical research for the prevention of AD. This discussion group included experts from academia, including AD researchers and bioethicists, patients’ organizations and regulatory agencies. This article summarizes the outcome of that meeting, where these ethical and policy challenges were debated and recommendations to address them throughout the research process were proposed, discussed, and agreed.

2. The scientific basis of the preclinical stage and prevention strategies

The prevailing hypothesis for AD pathogenesis, the amyloid cascade hypothesis, assumes several causal events that begin with the accumulation of β-amyloid in the brain followed by tau hyperphosphorylation and then neuronal degeneration. In addition to advanced age, the risk of developing AD is increased among persons with certain genetic variants. Autosomal dominant AD (ADAD), characterized by pathogenic mutations in one of three genes—the β-amyloid precursor protein (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2)—provide almost certain risk (~100%) of developing symptomatic AD [17]. In addition, apolipoprotein E e4 (APOE e4) allele carriers have a significantly higher risk of developing symptomatic AD when compared to noncarriers [18]. Specifically, the risk of AD has been shown to be 2.6 times higher for people with the APOE ε2/ε4 genotype relative to APOE ε3/ε3 individuals and 3.2 and 14.9 times higher for APOE ε3/ε4 and APOE ε4/ε4 persons, respectively [19].

Our understanding of preclinical AD indicates that biomarker abnormality occurs in a temporal manner where it has been demonstrated that abnormally low cerebrospinal fluid (CSF) β-amyloid 42 (Aβ42) and cerebral amyloid deposits precede elevated CSF tau, topographical cerebral injury, and cognitive decline [20]. New data from recently initiated studies such as EPAD (European Prevention of Alzheimer’s Dementia), PREVENT Research Programme
(UK and France), and ALFA (Alzheimer and Family; Spain) will further support these disease models. The timeframe for these pathologic changes may be as long as 25 years before symptom onset. In presymptomatic ADAD individuals, CSF \( A_{\beta 42} \) decline has been observed 25 years before clinical symptoms, whereas \( \beta \)-amyloid deposition (measured by amyloid imaging) and elevated CSF tau have been detected 15 years before symptom onset [9]. The preclinical stage of AD can be further subdivided into three stages: stage 1—asymptomatic amyloidosis (positive amyloid imaging, low CSF \( A_{\beta 42} \)); stage 2—amyloidosis and neurodegeneration (neuronal dysfunction; high CSF tau); and stage 3—amyloidosis, neurodegeneration, and subtle or subjective cognitive decline (this decline has yet to be operationalized but presumably falls short of prodromal AD or MCI due to AD) [8]. The validity of these stages has been suggested by a retrospective study of asymptomatic individuals which demonstrated that the 5-year progression rate was 2% for participants classified as normal, 11% for those in stage 1, 26% for stage 2, and 56% for stage 3 [14].

Retrospective and prospective studies are useful to indicate the likely causal pathways that lead from a healthy aging brain to a diseased brain, but they cannot definitively establish the validity of these pathways. The best method to establish this validity is to intervene using a randomized and controlled experiment with an antiamyloid drug in asymptomatic persons who exhibit amyloid-positive PET scans, before substantial loss of synaptic and neuronal integrity. In that sense, the only way to validate the causality of a pathway is through a clinical trial in which the active drug is able to prevent the deleterious effect of the proposed pathogenic process. Hence, a positive prevention trial not only validates the efficacy of the drug but also the causality of the treated pathway. This model has been used in other diseases where treatment in asymptomatic individuals has resulted in significant benefit for patients and society. For instance, in the United States, 28% of the population aged 40 years and over uses cholesterol-lowering medication on a regular basis. The appropriate widespread use of these medications has with no doubt prolonged the lives of millions [21]. The origin of these drugs was a pioneer study in asymptomatic familial hypercholesterolemia patients [22].

In our field, to arrest or at least delay, the onset of cognitive decline in subjects showing amyloid accumulation is termed secondary prevention. On the other hand, primary prevention strategies directed toward preventing the initial cortical amyloid deposition would significantly impact the prevalence of AD. Secondary prevention clinical trials in persons with preclinical AD that are biomarker positive and asymptomatic are already occurring and summarized here in Table 1 [23–26]. Collectively, these studies will help ascertain if secondary prevention is a valid approach for AD, and whether clinical trials of 3 to 5 years are sufficient for delaying cognitive decline [27]. Recent worldwide initiatives are also aiming to maximize efficiency to obtain a clinical signal and develop sensitive outcomes for detecting early decline, through new trial designs. The first of these initiatives, funded by the Innovative Medicines Initiative under the topic “European platform for proof of concept for prevention in Alzheimer’s disease” is the EPAD project. This project aims at delivering an adaptive trial for secondary prevention of AD. Sister initiatives in the upcoming years will be launched in the United States and Canada.

The motivation for secondary prevention trials in AD dementia is based on the observation that delaying the onset of AD dementia by as little as 5 years would decrease the total number of Americans aged 65 years and older with AD from 5.6 million in 2010 to 4 million by 2020 [28]. Longitudinal studies have shown that as many as 30%–40% of elderly healthy individuals exhibit signs of \( \beta \)-amyloid accumulation [29]. In addition, many individuals with \( \beta \)-amyloid and tau accumulation exhibited subtle cognitive decline antemortem [30]. Furthermore, several studies have also shown that cognitively normal individuals with abnormal levels of AD biomarkers exhibit longitudinal cognitive decline [31,32]. These individuals are at an increased risk for progressing to cognitive impairment [33,34].

3. The ethical challenges

When considering preclinical AD trials, two ethical issues of special importance arise. First, because asymptomatic persons are exposed to novel agents for an extended period, the design of the trial must ensure that the potential benefits justify the burden and risk for the participants. Second, many prevention trials will enrich their study population through genetic and other biological risk factors that will be screened by genetic and/or imaging techniques. As these tests are normally discouraged in routine clinical practice and therefore, a person would not normally receive this information unless participating in prevention trials, the issue of disclosure of such information must be carefully addressed [35–37].

3.1. Risk-benefit considerations

One of the issues we face when considering the clinical therapeutic window for preclinical studies is that the earlier we are in the disease process, the longer clinical trials aimed to detect change will have to last. On a practical level, this will result in screening an increased number of participants to find the right population and longer follow-up times to detect change. For example, the A4 study estimates that to enroll over 1000 individuals, over 5000 people must be screened, around 3000 will have to undergo PET amyloid imaging, and that it will take 3 years to detect any effect of the treatment [25]. If future longitudinal studies in preclinical individuals involve widening the biomarker
status to incorporate individuals with lower biomarker levels, the number of participants needed and the length of follow-up are likely to increase. Overall, future longitudinal studies that prolong participants’ exposure to interventions will place a significantly greater procedural burden on individuals; the longer these studies last, the greater the procedural burden will be. Based on the current biomarker technologies and the regulatory landscape, enrolling participants with even lower levels of β-amyloid accumulation (compared to current studies) will require an evaluation of what level of risk is ethical to offer as a potential exposure.

One important factor in determining the acceptable risk-benefit ratio is to better understand the public’s values regarding this issue. However, this will require improving public understanding of the relevant issues, such as the probabilistic over deterministic nature of biomarkers. This may be accomplishable through public messaging and other educational methods. Indeed, the history of developing promising drugs while limiting the hazard to patients who take these medications.” In a similar manner, input from the patient community can help the AD research community understand what degree of risk is acceptable when drugs may, for example, present risks to brain function from side effects such as amyloid-related imaging abnormalities.

A basic ethical principle in clinical research is “respect for persons”, recognizing that some individuals are not autonomous, which sometimes can be the case among Alzheimer’s patients. The requirement for informed consent is designed to uphold this ethical principle and is based on clear language and unbiased information on the issue at stake. One benefit of conducting trials in preclinical AD (over studies with symptomatic individuals) is that asymptomatic persons are in a much better position to protect their own welfare and to express their values regarding what risk is acceptable for them in providing informed consent. We know that people volunteer for clinical trials for a variety of reasons and indeed, the distinct types of benefit outcomes from research (namely direct, collateral, and aspirational) must be specifically specified when obtaining the participants informed consent [40]. One perceived benefit of interventional trials is the possibility of receiving an efficacious therapeutic agent or combination of agents/interventions (direct benefit). Hence, individuals enroll in research because they consider it may be of benefit to their own health, and this benefit outweighs the risks of the research. Furthermore, there may be associated indirect potential benefits for clinical trial participation (collateral benefit). For example, participation may yield positive psychological impact on self-confidence, self-worth, and the perceived benefit that the volunteer provides societal value [41] and even free physical examination and testing. In addition, it has also been shown that altruism (aspirational
benefit)—that is, potential benefit to their relatives, to future sufferers or to society—also may be a perceived benefit of entering a clinical trial [42].

3.2. Disclosure of risk marker status

Another fundamental consideration that is integral in the ethical assessment of clinical research is the potential harm and benefit of disclosure [35–37]. Although genetic testing and biomarker status differ in several ways such as imminence of risk, stability of the results, and direct implications for consanguineous family members [37], disclosure of any genetic or biomarker status is a complex task that requires specific training and ability to convey uncertainty. Therefore, discussing the risks and benefits of disclosure can largely be regarded as indistinguishable between genetic and biomarker disclosure. It has already been shown that knowledge imbalances between scientific and medical concepts related to genetics as well as medical practices can occur, even in study populations with a relatively high educational status and genetic knowledge [43]. When considering disclosure, the physician or researcher has the responsibility of educating the patient on the risks and benefits of learning their genetic/biomarker status. In the Risk Evaluation and Education of AD (REVEAL) study, pictures, graphic illustrations, and animations are used to explain the risk of developing AD, especially in cases when there is a genetic predisposition [44,45].

The decision to learn one’s genetic or biomarker status is that of the study participant, especially in trials in which participants are cognitively normal. From an ethical standpoint, the concern with disclosing a person’s biomarker status is that this could induce psychological stress. Previous studies that have examined the impact of genetic disclosure have found that there are no overall significant differences in the levels of anxiety experienced by individuals who learn their APOE status compared to individuals who do not learn this information [46]. Nevertheless, those who were informed that they were APOE ε4 non-carriers had a significantly lower level of test-related distress. In this case, the study was performed over the course of 1 year; however, when considering preclinical studies that may last for many years during which participants are implicitly reminded of their genetic or biomarker status, the burden of knowing one’s status must be thoroughly studied for AD. In that sense, the preclinical and early diagnoses of Huntington’s disease (HD) are associated with an increased risk of suicidal behavior. On the other hand, this figure coincides with the suicide rates previously reported for symptomatic individuals diagnosed with HD [47]. Therefore, more studies are necessary to prevent this harm from being neglected.

Another consideration in whether to disclose genetic or biomarker results is the concept of a stereotype threat whereby providing a label to the individual elicits behavior and/or characteristics that are perceived as belonging to this label. This is illustrated in a recent study where APOE ε4 carriers who were told had poorer performances on cognitive tests compared to their nondisclosure counterparts who carried the same alleles [48].

Given the potential adverse effects of knowing one’s risk, should the AD research community always conduct trials that do not disclose gene or biomarker results? In answering this question, it is important to examine the public’s perception of predictive testing (with the assumption of receiving the results). An Alzheimer Europe survey of random samples from five different countries found that approximately two-thirds of respondents would get a medical test which would tell them whether they would get AD before they had symptoms [49]. In addition, other studies have shown that disclosure of an “at-risk” status can also positively impact peoples’ lives. Studies that followed-up disclosure groups found that APOE ε4 carriers more frequently took measures to reduce risk, compared to APOE ε4 non-carriers, implementing health-related behavioral changes [50,51].

Research designs that disclose risk information can further protect subjects by implementing safeguards. Before disclosing genetic or biomarker status, the investigator ought to assess if the potential participant is emotionally capable of enrolling in a study. Data from the REVEAL study clearly show that those who exhibited a high degree of emotional stress before undergoing genetic testing were more likely to have emotional difficulties after disclosure [46], although this does not preclude those subjects for participating in a study. Furthermore, for those who are included, one way to reduce potential stress is to provide continuous counseling throughout the study or through social forums where open discussions can take place as this has been shown to have a direct positive effect on stress and anxiety [52].

Briefly, the main risks deriving from disclosure include placing a cloud of uncertainty over participants that may affect their daily lives and/or performance in specific procedures and the complexity of conveying uncertainty. On the other hand, main benefits comprise the protection of biomarker-negative individuals from risks and harms related to clinical studies’ procedures, and the positive impact that this information may have on people’s lives. According to these appreciations, we recommend to disclose or not biomarker status with attention to study type (observational studies vs clinical trials; see below).

When considering the prospect of long-term preclinical studies, we recommend that for observational studies, unless the aim of the study is to investigate the impact of disclosure on outcome, the most scientifically valid method is a blinded enrollment study in which genetic or biomarker status is not disclosed. This will avoid the impact of knowing on participants’ welfare and cognitive performance, together with disclosing clinically nonrelevant biomarker or genetic status of uncertain prognosis.
For interventional studies, protecting the subjects that are biomarker negative from risks and harms related to the trial’s procedures prevail over the motivations noted above to support blinded enrollment. Furthermore, a recent systematic analysis comparing the ethics of transparent (i.e., requiring disclosure) enrollment versus blinded enrollment in AD prevention studies provided strong arguments that there are no special risk benefit, informed consent, or fair participant selection issues that require blinded enrollment. Therefore, if it is feasible to conduct a scientifically valid trial with a transparent enrollment study design, we recommend this design for interventional studies. Exceptionally, the feasibility of a transparent design will depend on the characteristics of the study population. In the DIAN-TU study, the potential participant pool is quite small consisting of relatively young persons at risk for familial AD. For such persons, whether to learn that they will almost certainly develop AD at a relatively young age is a very momentous and complex question. It has been the case that even when offered the opportunity to have genetic counseling and commercial genetic testing to learn their mutation status at no cost to themselves, the majority decline as they do not wish to know, as has been the case in similar populations in previous studies [53–55]. Thus, it would not be feasible to conduct a scientifically valid study involving DIAN-TU registry participants using a transparent enrollment (i.e., requiring disclosure of genetic status).

By contrast, the A4 trial draws from a large pool of potential participants who have an elevated probabilistic increase in risk for AD and requires that the participants are willing to learn their amyloid biomarker status. Most of the participants are in a much later stage of life and may in fact have a greater motivation to learn about factors that may increase their risk of AD. Thus, the feasibility of a transparent enrollment design is much greater. This has been confirmed in our experience so far in the A4 trial [56,57].

An important additional argument for the transparent design (i.e., requiring gene or biomarker disclosure) is that this design better reflects the future clinical practice of drug prescription to those who learn that they have an altered AD biomarker. A design that includes biomarker disclosure would therefore more closely resemble routine clinical practice and so can provide information about the success of this potential clinical future. Furthermore, blinded designs require risk-negative participants to be enrolled to avoid “disclosure by enrollment”; thus, transparent enrollment has the advantage of minimizing the number of participants enrolled to attain sufficient statistical power to obtain clinically meaningful results. New trials currently under design, like the new API trial with APOE ε4/ε4 homozygotes, will be disclosing APOE status, through a standardized genetic counseling protocol [46].

Finally, we know that AD manifests its pathology years before it manifests its clinical symptoms and hence, from a biological perspective, the disease is already present and the term preclinical AD is accurate. Nevertheless, we have to be especially careful in how we address and communicate the preclinical stage of the disease to study participants. Taking into account that not all participants in preclinical studies will develop the clinical symptoms of the disease, one useful term to address them could be asymptomatic at risk for cognitive impairment.

4. Social, legal, and policy challenges

The foremost ethical obstacle that we, as a society, need to overcome involves the concept of social justice—namely, justice in terms of the distribution of wealth, opportunities, and privileges within a society. Can one therefore justify secondary prevention as a priority for the public administration when there is insufficient support and treatment for individuals that suffer from dementia? Indeed, we envisage that conducting trials in preclinical AD will increase the overall awareness of AD that should, in turn, improve support and treatment for current AD sufferers. Nevertheless, currently, between half and three quarters of people with dementia have no formal diagnosis [58–60]. Furthermore, for those that are diagnosed with AD many do not receive their diagnosis, and for those that do it there can be a substantial delay between diagnostic tests and receiving the diagnosis [61,62]. In a recent special report of the Alzheimer’s Association Facts & Figures, only 45% of individuals diagnosed with Alzheimer’s disease were notified of their diagnosis.

The first step to achieve this is the need to develop a uniform language (currently under development by expert committees through both the Alzheimer’s Association and Alzheimer’s Europe) to reinforce a single message to the public and policy makers. By unifying the message from clinical research, we can increase the awareness of AD clinical trials taking place. Increasing awareness will improve public understanding toward the severity of the disease as it has been shown that individuals with close personal ties to patients with AD are more likely (than those without) to view AD as a major concern [63]. Consequently, this will not only reduce the number of undiagnosed individuals but will also serve to improve willingness to pursue predictive genetic and biomarker testing that may facilitate future asymptomatic enrollment.

Changing the public perception of AD and predictive testing also requires the introduction of legal changes to protect prospective participants. Currently, there is limited protection for individuals who wish to participate in preventative clinical trials. For example, in the United States, the Genetic Information Nondiscrimination Act (GINA) prohibits discrimination by health insurers or employers based on genetic information. GINA protects individuals with known genetic markers who have not demonstrated “disease manifestation” of a condition that is consistent with the genetic marker [64]. By contrast,
European protection of an individual’s genetic information differs among governments [65]. The legal mechanisms for reacting against breaches of the right to privacy in Europe are based on Directive 95/46/CE. However, this Directive has been differently transposed in different member states. Although in some countries (such as Belgium, Spain, and the Netherlands), privacy is recognized as a constitutional right, others such as Germany, Italy, Denmark, and France do not have this specific recognition.

At present, there are no legal safeguards that protect an individual’s biomarker data and without adequate protection, the prospect of participating in a secondary prevention trial may significantly impact an individual’s ability to have access to an adequate health insurance, insurance coverage, and working potential. To implement change, governmental bodies will need to first recognize biomarkers through policy bodies such as the FDA (Food and Drug Administration) and EMA (European Medicines Agency). At the time of writing, both the FDA and the EMA are preparing guidelines on the use of biomarkers in AD preclinical research. The outcome of these efforts will play an important role in future health and legal policy for AD research. In addition, current prevention studies, together with future ones, will provide information of the meaning of a positive beta-amyloid PET scan that may change with the gain of further knowledge, and education about the risks and benefits of beta-amyloid PET imaging, assess the participant’s readiness and willingness to receive the result and, where positive results are disclosed, monitor the individual’s well being. An investigator taking part in such research has the responsibility to make sure that the study is taking steps to minimize disclosure of the result in the medical record, and the participant should feel free to ask whether this is the case.

One final challenge that faces the future of trials in preclinical AD is the financial cost of such research initiatives. The patent life gives the manufacturer a maximum of 20 years of exclusive ownership since initial filing. If preclinical AD trials are to last around 5 years, the likelihood that pharmaceutical companies can fund them and achieve profit from successful therapeutic agents is improbable. Therefore, it is very likely that public financial support will be required to complement private funding to support future AD clinical trials. Developments to tackle this challenge are already a reality in the United States and Europe. In the United States, both DIAN-TU [23] and API are the result of a public-private partnership; whereas in Europe, the EPAD project aims to deliver a standing, adaptive, multiarm proof of concept study for early and accurate decisions on a candidate compound’s (or combination of compounds) ongoing development for the prevention of Alzheimer’s dementia [66]. We reason that such distributed infrastructures that support clinical research for societal gain will be essential for the future of AD research.

5. Conclusions

Studies and trials in preclinical AD have a solid scientific basis and hold significant promise as part of the future AD research landscape. In this scenario, a number of ethical challenges, mainly related to determining appropriate risk-benefit ratios and disclosing individuals’ biomarker status, arise. Determining the acceptable risk-benefit ratio will require improving public understanding of the relevant issues, such as the probabilistic over deterministic nature of biomarkers. Finally, we consider that both blinded observational trials and transparent interventional trials should be considered as standard for future studies in this field.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional sources. Publications validating pathophysiological Alzheimer’s disease (AD) biomarkers and longitudinal studies on Alzheimer’s pathology that justify the performance of preclinical studies are cited throughout the manuscript.

2. Interpretation: We identify ethical concerns from asymptomatic AD studies related to risk-benefit ratio and genetic and biomarker disclosure as substantial ethical obstacles for preclinical studies. Asymptomatic individuals participating in clinical trials should be educated on the risks and benefits of participation in order to determine the ethically appropriate risk-benefit ratio.

3. Future directions: Public engagement, focus groups and social support using a unified vocabulary will be essential to improve standards of care for current AD sufferers and promote predictive testing. Such educational measures will be fundamental to overcome societal and legal obstacles and protect individuals from discrimination.
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