



5-1-2016

# Ethical Challenges in Preclinical Alzheimer's Disease Observational Studies and Trials: Results of the Barcelona Summit

Jose L. Molinuevo

Jordi Cami

Xavier Carne

Maria C. Carrillo

Jean Georges

*See next page for additional authors*

---

## Recommended Citation (OVERRIDE)

Ethical challenges in preclinical Alzheimer's disease observational studies and trials: Results of the Barcelona summit By: Molinuevo, Jose L.; Cami, Jordi; Carne, Xavier; et al. ALZHEIMERS & DEMENTIA Volume: 12 Issue: 5 Pages: 614-622 Published: MAY 2016

This paper is posted at Scholarly Commons. [http://repository.upenn.edu/neuroethics\\_pubs/142](http://repository.upenn.edu/neuroethics_pubs/142)  
For more information, please contact [repository@pobox.upenn.edu](mailto:repository@pobox.upenn.edu).

---

# Ethical Challenges in Preclinical Alzheimer's Disease Observational Studies and Trials: Results of the Barcelona Summit

## 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

## Disciplines

Bioethics and Medical Ethics | Neuroscience and Neurobiology | Neurosciences

## Author(s)

Jose L. Molinuevo, Jordi Cami, Xavier Carne, Maria C. Carrillo, Jean Georges, Maria B. Isaac, Zaven Khachaturian, Scott Y. H. Kim, John C. Morris, Florence Pasquier, Craig Ritchie, Reisa Sperling, and Jason Karlawish

Perspective

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

José L. Molinuevo<sup>a,\*</sup>, Jordi Cami<sup>b</sup>, Xavier Carné<sup>c</sup>, Maria C. Carrillo<sup>d</sup>, Jean Georges<sup>e</sup>,  
Maria B. Isaac<sup>f</sup>, Zaven Khachaturian<sup>g</sup>, Scott Y. H. Kim<sup>h</sup>, John C. Morris<sup>i</sup>, Florence Pasquier<sup>j</sup>,  
Craig Ritchie<sup>k</sup>, Reisa Sperling<sup>l</sup>, Jason Karlawish<sup>m</sup>

<sup>a</sup>Barcelonaβeta Brain Research Center, Pasqual Maragall Foundation, Barcelona, Spain

<sup>b</sup>Pompeu Fabra University and Pasqual Maragall Foundation, Barcelona, Spain

<sup>c</sup>Clinical Pharmacology Department, Hospital Clinic and IDIBAPS, Barcelona, Spain

<sup>d</sup>Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA

<sup>e</sup>Alzheimer Europe, Luxembourg, Luxembourg

<sup>f</sup>European Medicines Agency (EMA), London, UK

<sup>g</sup>The Campaign to Prevent Alzheimer by 2020 (PAD2020), Potomac, MD, USA

<sup>h</sup>Department of Bioethics, Clinical Center, National Institutes of Health, Bethesda, MD, USA

<sup>i</sup>Washington University School of Medicine, St Louis, MO, USA

<sup>j</sup>Inserm 1171, Université Lille2, CHU, Memory Centre Lille, Lille, France

<sup>k</sup>Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

<sup>l</sup>Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

<sup>m</sup>Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

### 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.

© 2016 The Authors. Published by Elsevier Inc. on behalf of Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Keywords:** Alzheimer's disease; Preclinical AD; Ethics; Asymptomatic

The authors' personal views should not be understood or quoted as being made on behalf of or reflecting the official position or policies of the NIH, the DHHS, the US Government, the European Medicines Agency, or any of their committees or working parties.

J.L.M. has provided scientific advice or has been an investigator or data monitoring board member receiving consultancy fees from Novartis, Pfizer, Eisai, Janssen-Cilag, Lundbeck, Roche, Bayer, Bristol-Myers Squibb, GE Health Care, Merz, MSD, GlaxoSmithKline, Astra-Zeneca, Avid, Lilly, Boehringer-Ingelheim, Biokit, Piramal, IBL, and Fujirebio-Europe. Neither J.C.M. nor his family own stock or have equity interest (outside mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company. J.C.M. has participated or is currently partici-

pating in clinical trials of antedementia drugs sponsored by the following companies: Janssen Immunotherapy, Pfizer, Eli Lilly/Avid Radiopharmaceuticals, SNIFF (The Study of Nasal Insulin to Fight Forgetfulness) study, and A4 (the anti-amyloid treatment in asymptomatic Alzheimer's disease) trial. J.C.M. has served as a consultant for Lilly USA, ISIS Pharmaceuticals, and Charles Dana Foundation. He receives research support from Eli Lilly/Avid Radiopharmaceuticals and is funded by NIH grants #P50AG005681; P01AG003991; P01AG026276; and U19AG032438.

\*Corresponding author. Tel.: +34 93 316 0990; Fax: +34 93 316 0996.  
E-mail address: [jlmolinuevo@fpmaragall.org](mailto:jlmolinuevo@fpmaragall.org)

## 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  $\beta$ -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- $\beta$  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  $\beta$ -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  $\beta$ -amyloid precursor protein (*APP*), Presenilin 1 (*PSEN1*), and Presenilin 2 (*PSEN2*)—provide almost certain risk ( $\sim 100\%$ ) of developing symptomatic AD [17]. In addition, apolipoprotein E  $\epsilon 4$  (*APOE*  $\epsilon 4$ ) 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*  $\epsilon 2/\epsilon 4$  genotype relative to *APOE*  $\epsilon 3/\epsilon 3$  individuals and 3.2 and 14.9 times higher for *APOE*  $\epsilon 3/\epsilon 4$  and *APOE*  $\epsilon 4/\epsilon 4$  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)  $\beta$ -amyloid 42 ( $A\beta_{42}$ ) 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 anti-amyloid 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

Table 1  
Secondary prevention clinical trials in Alzheimer's disease

Descriptor	DIAN-TU	API-ADAD	A4	TOMMORROW	API-APOe4
Target population	Autosomal dominant AD	Autosomal dominant AD	Cognitively normal, beta-amyloid positive	Cognitively normal with genetic risk	Cognitively normal with genetic risk
Specific characteristics	ADAD mutation carriers	<i>PSEN1 E280 A</i> mutation carriers	Positive brain amyloid PET	<i>TOMM40/APOE</i> genotype	Homozygous <i>APOe4</i> genotype
Estimated enrollment	210	300	1150	5800	1340
Phase	Phase II/III	Phase II	Phase III	Phase III	Phase II/III
Compound	Gantenerumab, Solanezumab	Crenezumab	Solanezumab	Pioglitazone	CAD106, CNP520
Mechanism	Anti-A $\beta$ antibodies	Anti-A $\beta$ antibody	Anti-A $\beta$ antibody	PPAR- $\gamma$ agonist	A $\beta$ vaccine & BACE inhibitor
Status	Recruiting	Recruiting	Recruiting	Recruiting	Not yet recruiting
Primary outcome	Composite cognitive test score	Composite cognitive test score	Composite cognitive test score	Time to diagnosis of MCI due to AD	Time to diagnosis of MCI due to AD, composite cognitive test score
Study duration	4 years	5 years	3 years	5 years	5 years
Study identifier	NCT01760005	NCT01998841	NCT02008357	NCT01931566	NCT02565511
Reference	Moulder et al., 2013 [23]	Reiman et al., 2011 [24]	Sperling et al., 2014 [25]	Roses et al., 2014 [26]	Reiman et al., 2011 [24]

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  $\beta$ -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 treatments for serious and life threatening disease such as AIDS and multiple sclerosis (MS) shows how decisions about what risks are acceptable in the pursuit of a treatment are part of a negotiated social order that engages expert clinicians, regulators, and patients. In the case of AIDS, the patient community moved trialists and regulators to adopt trial designs that might expose subjects to more active intervention-derived risk but at the same time expedited the discovery of whether an intervention was effective [38]. Input from patient advocates was also influential in the FDA's decision to permit natalizumab as a treatment for MS despite the risk of progressive multifocal leukoencephalopathy ([39]; note "There is an active ongoing discussion among regulators, researchers, and patient advocates seeking successful ways to continue development of

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*  $\epsilon 4$  noncarriers 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*  $\epsilon 4$  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*  $\epsilon 4$  carriers more frequently took measures to reduce risk, compared to *APOE*  $\epsilon 4$  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*  $\epsilon 4/\epsilon 4$  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.

## Acknowledgments

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115736, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in kind contribution. The authors thank Karine Fauria and Carolina Minguillón for their assistance with this article preparation and for the logistical planning of the summit. They thank as well the institutions that have supported the realization of the summit: "Obra social la Caixa" for the summit venue at "Caixa Forum"; Roche, Novartis, Lilly, Lumbeck, and Janssen for logistic support; and the Pasqual Maragall Foundation for the summit organization. The authors of this article presented and discussed their views throughout the meeting.

## 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.

## References

- [1] Alzheimer's Disease International. Policy Brief for Heads of Government: The Global Impact of Dementia 2013–2050. London: Alzheimer's Disease International; 2013.
- [2] Giacobini E, Gold G. Alzheimer disease therapy—moving from amyloid- $\beta$  to tau. *Nat Rev Neurol* 2013;9:677–86.
- [3] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–44.
- [4] Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007;6:734–46.
- [5] Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010;9:1118–27.
- [6] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9.
- [7] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:270–9.
- [8] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, 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. *Alzheimers Dement* 2011;7:280–92.
- [9] Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 2012;367:795–804.
- [10] Knopman DS, Jack CR Jr, Wiste HJ, Weigand SD, Vemuri P, Lowe V, et al. Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. *Neurology* 2012;78:1576–82.
- [11] Mormino EC, Betensky RA, Hedden T, Schultz AP, Ward A, Huijbers W, et al., Alzheimer's Disease Neuroimaging Initiative. Amyloid and APOE epsilon4 interact to influence short-term decline in preclinical Alzheimer disease. *Neurology* 2014;82:1760–7.
- [12] Reiman EM, Quiroz YT, Fleisher AS, Chen K, Velez-Pardo C, Jimenez-Del-Rio M, et al. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case-control study. *Lancet Neurol* 2012;11:1048–56.
- [13] Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol* 2013;12:357–67.
- [14] Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol* 2013;12:957–65.
- [15] Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther* 2014;6:37.
- [16] Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283:2701–11.
- [17] Bateman RJ, Aisen PS, De Strooper B, Fox NC, Lemere CA, Ringman JM, et al. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther* 2011;3:1.
- [18] Hauser PS, Ryan RO. Impact of Apolipoprotein E on Alzheimer's Disease. *Curr Alzheimer Res* 2013;10:809–17.
- [19] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *JAMA* 1997;278:1349–56.
- [20] Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013;12:207–16.
- [21] Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013;1:CD004816.
- [22] Haba T, Mabuchi H, Yoshimura A, Watanabe A, Wakasugi T, Tatami R, et al. Effects of ML-236b (compactin) on sterol synthesis and low density lipoprotein receptor activities in fibroblasts of patients with homozygous familial hypercholesterolemia. *J Clin Invest* 1981;67:1532–40.
- [23] Moulder KL, Snider BJ, Mills SL, Buckles VD, Santacruz AM, Bateman RJ, et al. Dominantly Inherited Alzheimer Network: facilitating research and clinical trials. *Alzheimers Res Ther* 2013;5:48.
- [24] Reiman EM, Langbaum JB, Fleisher AS, Caselli RJ, Chen K, Ayutyanont N, et al. Alzheimer's Prevention Initiative: a plan to accelerate the evaluation of presymptomatic treatments. *J Alzheimers Dis* 2011;26(Suppl 3):321–9.
- [25] Sperling RA, Rentz DM, Johnson KA, Karlawish J, Donohue M, Salmon DP, et al. The A4 Study: Stopping AD before Symptoms Begin? *Sci Transl Med* 2014;6:228fs13.
- [26] Roses AD, Saunders AM, Lutz MW, Zhang N, Hariri AR, Asin KE, et al. New applications of disease genetics and pharmacogenetics to drug development. *Curr Opin Pharmacol* 2014;14:81–9.
- [27] Vellas B, Carrillo MC, Sampaio C, Brashear HR, Siemers E, Hampel H, et al. Designing drug trials for Alzheimer's disease: What we have learned from the release of the phase III antibody trials: A report from the EU/US/CTAD Task Force. *Alzheimers Dement* 2013;9:438–44.
- [28] OECD (2014), “Unleashing the Power of Big Data for Alzheimer's Disease and Dementia Research: Main Points of the OECD Expert Consultation on Unlocking Global Collaboration to accelerate Innovation for Alzheimer's Disease and Dementia”, OECD Digital Economy Papers, No. 233, OECD Publishing, <http://dx.doi.org/10.1787/5jz73kvmvbw-en>.
- [29] Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol* 2008;65:1509–17.
- [30] Price JL, McKeel DW, Buckles VD, Roe CM, Xiong C, Grundman M, et al. Neuropathology of nondemented aging: Presumptive evidence for preclinical Alzheimer disease. *Neurobiol Aging* 2009;30:1026–36.
- [31] Landau SM, Mintun MA, Joshi AD, Koeppe RA, Petersen RC, Aisen PS, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Ann Neurol* 2012;72:578–86.
- [32] Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: Measuring amyloid-related decline. *JAMA Neurol* 2014;71:961–70.
- [33] Roe CM, Fagan AM, Grant EA, Hassenstab J, Moulder KL, Maue Dreyfus D, et al. Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. *Neurology* 2013;80:1784–91.
- [34] Rowe CC, Bourgeat P, Ellis KA, Brown B, Lim YY, Mulligan R, et al. Predicting Alzheimer disease with  $\beta$ -amyloid imaging: Results from the Australian imaging, biomarkers, and lifestyle study of ageing. *Ann Neurol* 2013;74:905–13.
- [35] Kim SY, Karlawish J, Berkman BE. Ethics of genetic and biomarker test disclosures in neurodegenerative disease prevention trials. *Neurology* 2015;84:1488–94.

- [36] Lingler JH, Klunki WE. Disclosure of amyloid imaging results to research participants: Has the time come? *Alzheimers Dement* 2013; 9:741–7442.
- [37] Roberts JS, Dunn LB, Rabinovici GD. Amyloid imaging, risk disclosure and Alzheimer's disease: ethical and practical issues. *Neurodegener Dis Manag* 2013;3:219–29.
- [38] Epstein S. *Impure Science: AIDS, Activism and the Politics of Knowledge*. Oakland, CA: UC Press; 1998.
- [39] Rudick R, Polman C, Clifford D, Miller D, Steinman L. Natalizumab: bench to bedside and beyond. *JAMA Neurol* 2013;70:172–82.
- [40] King N. Defining and Describing Benefit Appropriately in Clinical Trials. *J Law Med Ethics* 2000;28:332–43.
- [41] Albert SM, Sano M, Marder K, Jacobs DM, Brandt J, Albert M, et al. Participation in clinical trials and long-term outcomes in Alzheimer's disease. *Neurology* 1997;49:38–43.
- [42] Avent C, Curry L, Gregory S, Marquardt S, Pae L, Wilson D, et al. Establishing the motivations of patients with dementia and cognitive impairment and their carers in joining a dementia research register (DemReg). *Int Psychogeriatr* 2013;25:963–71.
- [43] Haga SB, Barry WT, Mills R, Ginsburg GS, Svetkey L, Sullivan J, et al. Public Knowledge of and Attitudes Toward Genetics and Genetic Testing. *Genet Test Mol Biomarkers* 2013;17:327–35.
- [44] Cupples LA, Farrer LA, Sadvnick AD, Relkin N, Whitehouse P, Green RC. Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: the REVEAL study. *Genet Med* 2004;6:192–6.
- [45] Lautenbach DM, Christensen KD, Sparks JA, Green RC. Communicating genetic risk information for common disorders in the era of genomic medicine. *Annu Rev Genomics Hum Genet* 2013;14:491–513.
- [46] Green RC, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T, et al. Disclosure of APOE Genotype for Risk of Alzheimer's Disease. *N Engl J Med* 2009;361:245–54.
- [47] Bird TD. Outrageous fortune: the risk of suicide in genetic testing for Huntington disease. *Am J Hum Genet* 1999;64:1289–92.
- [48] Lineweaver TT, Bondi MW, Galasko D, Salmon DP. Effect of Knowledge of APOE Genotype on Subjective and Objective Memory Performance in Healthy Older Adults. *Am J Psychiatry* 2014;171:201–8.
- [49] Alzheimer Europe - Research - Value of Knowing n.d. Available from: <http://www.alzheimer-europe.org/Research/Value-of-Knowing>. Accessed February 1, 2015.
- [50] Chao S, Roberts JS, Marteau TM, Silliman R, Cupples LA, Green RC. Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. *Alzheimer Dis Assoc Disord* 2008;22:94–7.
- [51] Vernarelli JA, Roberts JS, Hiraki S, Chen CA, Cupples LA, Green RC. Effect of Alzheimer disease genetic risk disclosure on dietary supplement use. *Am J Clin Nutr* 2010;91:1402–7.
- [52] Billings AG, Moos RH. Life stressors and social resources affect posttreatment outcomes among depressed patients. *J Abnorm Psychol* 1985;94:140–53.
- [53] Kolata G. How Do You Live Knowing You Might Have an Alzheimer's Gene? *The New York Times* 2012 June 7, 2012.
- [54] Ryman DC, Acosta-Baena N, Aisen PS, Bird T, Danek A, Fox NC, et al. Symptom onset in autosomal dominant Alzheimer disease: A systematic review and meta-analysis. *Neurology* 2014;83:253–60.
- [55] Steinbart EJ, Poorkaj P, Smith CO, Bird TD. Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. *Arch Neurol* 2001;58:1828–31.
- [56] Harkins K, Sankar P, Sperling R, Grill JD, Green RC, Johnson KA, et al. Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants. *Alzheimers Res Ther* 2015;7:26.
- [57] Sperling R, Karlawish J, Grill J, Burns J, Sultzer D, Johnson K, et al., for the Alzheimer's Disease Cooperative Study. Disclosing Amyloid Status in the Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease (A4) Study. Washington, USA: AAIC; 2015.
- [58] Löppönen M, Riihala I, Isoaho R, Vahlberg T, Kivelä S-L. Diagnosing cognitive impairment and dementia in primary health care – a more active approach is needed. *Age Ageing* 2003;32:606–12.
- [59] Boustani M, Peterson B, Hanson L, Harris R, Lohr KN, U.S. Preventive Services Task Force. Screening for dementia in primary care: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2003;138:927–37.
- [60] Valcour VG, Masaki KH, Curb JD, Blanchette PL. The detection of dementia in the primary care setting. *Arch Intern Med* 2000; 160:2964–8.
- [61] Alzheimer Europe - Alzheimer Europe - Our work - Completed projects - 2006: Dementia Carers' Survey n.d. Available from: <http://www.alzheimer-europe.org/Alzheimer-Europe/Our-work/Completed-projects/2006-Dementia-Carers-Survey>. Accessed November 27, 2014.
- [62] Bond J, Stave C, Sganga A, O'Connell B, Stanley RL. Inequalities in dementia care across Europe: key findings of the Facing Dementia Survey. *Int J Clin Pract Suppl* 2005;146:8–14.
- [63] Blendon RJ, Benson JM, Wikler EM, Weldon KJ, Georges J, Baumgart M, et al. The Impact of Experience with a Family Member with Alzheimer's Disease on Views about the Disease across Five Countries. *Int J Alzheimers Dis* 2012;2012:903645.
- [64] Arias JJ, Karlawish J. Confidentiality in preclinical Alzheimer disease studies When research and medical records meet. *Neurology* 2014; 82:725–9.
- [65] Coppieters Y, Levêque A. Ethics, privacy and the legal framework governing medical data: opportunities or threats for biomedical and public health research? *Arch Public Health* 2013;71:15.
- [66] Ritchie CW, Molinuevo JL, Truyen L, Satlin A, Van der Geysen S, Lovestone S, on behalf of the EPAD Consortium. Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. *Lancet Psychiatry* 2016;3:179–86.