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Alzheimer's Prevention Initiative: A Plan to Accelerate the Evaluation of Presymptomatic Treatments

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Abstract

There is an urgent need to find effective presymptomatic Alzheimer's disease (AD) treatments that reduce the risk of AD symptoms or prevent them completely. It currently takes too many healthy people, too much money and too many years to evaluate the range of promising presymptomatic treatments using clinical endpoints. We have used brain imaging and other measurements to track some of the earliest changes associated with the predisposition to AD. We have proposed the Alzheimer's Prevention Initiative (API) to evaluate investigational amyloid-modifying treatments in healthy people who, based on their age and genetic background, are at the highest imminent risk of developing symptomatic AD using brain imaging, cerebrospinal fluid (CSF), and cognitive endpoints. In one trial, we propose to study AD-causing *presenilin 1* [*PS1*] mutation carriers from the world's largest early-onset AD kindred in Antioquia, Colombia, close to their estimated average age at clinical onset. In another trial, we propose to study *apolipoprotein E* (*APOE*)*ε4* homozygotes (and possibly heterozygotes) close to their estimated average age at clinical onset. The API has several goals: 1) to evaluate investigational AD-modifying treatments sooner than otherwise possible; 2) to determine the extent to which the treatment's brain imaging and other biomarker effects predict a clinical benefit—information needed to help qualify biomarker endpoints for use in pivotal prevention trials; 3) to provide a better test of the amyloid hypothesis than clinical trials in symptomatic patients, when these treatments may be too little too late to exert their most profound effect; 4) to establish AD prevention registries needed to support these

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and other presymptomatic AD trials; and 5) to give those individuals at highest imminent risk of AD symptoms access to the most promising investigational treatments in clinical trials.

Keywords

brain imaging; cerebral spinal fluid; biomarkers; surrogate markers; presymptomatic Alzheimer's disease; early-onset Alzheimer's disease; late-onset Alzheimer's disease; presenilin 1; apolipoprotein E; clinical trials

Introduction

In this article, we note the urgent need to find effective presymptomatic Alzheimer's disease (AD) treatments, which we define as an intervention intended to postpone the onset, reduce the risk of, or completely prevent AD symptoms. We suggest that the greatest roadblock to the development of effective presymptomatic treatments may be the scientific means and financial incentives needed to evaluate the range of promising treatments. We briefly summarize relevant findings from our longitudinal study of cognitively normal people at three levels of risk for late-onset AD, which led us to propose how brain imaging and other biomarkers could be used to rapidly evaluate presymptomatic treatments in proof-of-concept clinical trials. We note the need for humility when it comes to predicting how these biomarkers will respond to AD-slowing treatments in clinical trials and point out that regulatory agencies are unlikely to approve a presymptomatic treatment based solely on biomarker endpoints until evidence is provided to show that a presymptomatic treatment's biomarker effects are reasonably likely to predict a clinical benefit. Finally, we describe our Alzheimer's Prevention Initiative (API), in which we intend to evaluate investigational amyloid-modifying treatments in cognitively normal people who, based on their age and genetic background, are at the highest imminent risk for symptomatic AD. The API is intended to evaluate treatments sooner than otherwise possible, to provide a better test of the amyloid hypothesis, to provide the evidence needed to show that an AD-modifying treatment's biomarker effects are reasonably likely to predict a clinical benefit, and give individuals at the highest imminent risk of symptomatic AD access to promising treatments in prevention trials.

"Presymptomatic (or Preclinical) AD Treatments:" A Proposed Definition

We have recently defined *presymptomatic* (or *preclinical*) *AD treatments"* as those interventions that are initiated before apparent cognitive decline and are intended to reduce the chance of developing AD-related symptoms[1]. The proposed term refers to an intervention whether it is started before or after biological evidence of the underlying disease (which may be hard to define), and whether it postpones the onset, partially reduces the risk of, or completely prevents symptomatic AD. We have introduced this term based on the United States Food and Drug Administration's (FDA's) stated view that it would not approve a treatment for the "prevention" of AD unless trials were able to demonstrate that a treatment prevented the onset of symptoms for the rest of a person's life, an impractically high hurdle to overcome. We believe that it will be easier to show that an intervention meets our proposed criterion as a presymptomatic or preclinical AD treatment and support regulatory agency approval. Our definition is also consistent with the research criteria for "preclinical AD treatment" recently proposed by a working group for the National Institute on Aging (NIA) and Alzheimer's Association[2].

Background

Alzheimer's disease is an unacceptable problem due to the toll it takes on patients and family caregivers, and the current and project financial impact on society[3,4]. A large number of healthy lifestyle interventions have been suggested but not yet proven to postpone the onset and reduce risk the risk of developing AD symptoms[5,6,7,8,9,10,11,12]. An even modestly effective therapy could have a significant public health benefit. For instance, a treatment that postponed the onset of AD symptoms by only five years without increasing life-expectancy might be able to reduce the number of clinically affected patients by half[4]. Meantime, a growing number of investigational disease-modifying treatments are in preclinical and clinical development[13], including but not limited to a large number of medication and immunization therapies intended to interfere with the production and accumulation of certain amyloid-β (Aβ) species. If, as many but not all researchers believe, the amyloid hypothesis is correct[14], if the treatment is targeting the Aβ species critically involved in the predisposition to symptomatic AD, if it is sufficiently safe and well tolerated, and if it is started sufficiently early, it might be possible to substantially reduce the risk of symptomatic AD and maybe even prevent it completely.

Unfortunately, it takes too many healthy people, too much money, and too many years—longer than a drug product's patent life—to evaluate presymptomatic treatments using clinical endpoints. For instance, in order to determine whether cholesterol-lowering, blood pressure-lowering or hormonal treatments reduced the risk of symptomatic AD if they were started in middle-age, when epidemiological studies suggest that they may have their most profound effect, nearly 50,000 healthy middle-aged research participants would be needed for a two-year placebo-controlled randomized clinical trial (RCT), such that a sufficient number of people developed symptomatic AD to detect a significant treatment effect. While there have been a small number of large, time-consuming prevention trials in older people[15,16,17,18], a new paradigm is needed to evaluate the range of presymptomatic treatments.

We believe that brain imaging or other biomarker measurements of AD are needed to rapidly evaluate presymptomatic treatments without having to study thousands of healthy volunteers or wait many years to characterize and compare clinical endpoints in the investigational and placebo treatment groups. Brain imaging and other biomarker methods continue to be further developed and used to detect and track changes associated with the clinical progression of AD, and several of these methods have been used to detect and track similar changes in the presymptomatic stages of AD[19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34]. Based on findings from the AD Neuroimaging Initiative (ADNI) and other longitudinal studies, researchers have established standardized procedures for the acquisition of brain imaging data and biological samples, to provide common data sets that have helped researchers further develop, test and compare their data analysis methods, and to provide sample size estimates for the use of biomarker endpoints and enrichment strategies for clinical trials, particularly in patients in the symptomatic stages of AD[35]. To date, the best established biomarkers of AD are fluorodeoxyglucose positron emission tomography (FDG PET) measurements of decline in the regional cerebral metabolic rate for glucose (rCMRgl), volumetric magnetic resonance imaging (MRI) measurements of regional or whole brain shrinkage, PET measurements of fibrillar amyloid-β (Aβ) burden, and low cerebrospinal fluid (CSF) $A\beta_{42}$ levels, alone or in combination with high CSF total tau or phospho-tau levels[24,1].

As noted below, we have suggested that biomarker endpoints could be used in proof-of-concept RCTs to rapidly evaluate presymptomatic treatments in cognitively normal people at increased risk for AD, and we have provided preliminary sample sizes estimates for some

of these trials[36,20]. Unfortunately industry partners are unlikely to provide financial support for these studies until the biomarker endpoints are qualified for use in pivotal trials. While the field needs the scientific means (i.e., biomarker endpoints) to rapidly evaluate presymptomatic treatments, it also needs the right financial incentive (i.e., regulatory agency qualification of the biomarker endpoints for use in the accelerated approval of presymptomatic AD treatments).

Regulatory agencies are unlikely to provide accelerated approval for a presymptomatic treatment based solely on biomarker (i.e., surrogate marker) endpoints without additional evidence to show that a treatment's biomarker effects are "reasonably likely" to predict a clinical benefit[37,38,39,40,41]. We believe that each of the most promising biomarker measurements should be included in clinical trials of AD-modifying treatments in order to show the extent to which an AD-modifying treatment moves the biomarkers, the extent to which the treatment moves the biomarkers in the right direction, and the extent to which a treatment's biomarker effects predict a clinical benefit[24,1].

Regulatory agencies may require evidence from presympomatic AD trials themselves to demonstrate the presymptomatic AD treatment's biomarker effects are reasonably likely to predict a clinical benefit. On one hand, biomarkers are needed to evaluate presymptomatic treatments in a rapid and cost-effective way. On the other hand, clinically proven treatments are needed to help qualify biomarkers for use as reasonably likely surrogate endpoints. Among other things, the API is intended to help resolve this apparent catch-22. We propose to characterize and compare the effects of an amyloid-modifying treatment on FDG PET, volumetric MRI, fibrillar amyloid PET and CSF endpoints in cognitively normal people who, based on their age and genetic background, are at the highest imminent risk of symptomatic AD. If, after two years, the treatment fails to move one or more of the biomarkers in the right direction, the Data Safety Monitoring Board (DSMB) would declare futility and the research participants would be eligible to participate in another trial. If, however, the treatment does have the predicted biomarker effects, the trial would be continued long enough to detect an effect on pre-specified cognitive endpoints.

Before we describe the API in more detail, we briefly summarize relevant biomarker and cognitive findings from our ongoing longitudinal study of cognitively normal people with two copies, one copy and no copies of the *apolipoprotein E (APOE) ε4* allele, the major late-onset AD susceptibility gene[42].

Preliminary Findings

In 1994, we initiated a longitudinal brain imaging study of cognitively normal, initially late-middle-aged, cognitively normal *APOEε4* homozygotes, heterozygotes, and non-carriers, reflecting three levels of genetic risk for late-onset AD, who were initially matched for their gender, age and educational level. Our subjects are followed every two years using FDG PET, volumetric MRI, and a battery of neuropsychological and clinical tests. In the last few years, they have begun to be following using fibrillar amyloid-β (Aβ) PET measurements, additional MRI measurements, and additional cognitive assessments; their DNA has been used to provide genome-wide association data, and they have begun to provide serum and plasma samples for use in ongoing and future analyses; and most recently, some have begun to provide CSF samples.

Of particular relevance to the API, we have demonstrated associations between *APOE ε4* gene dose (i.e., three levels of genetic risk for AD) and a) baseline reductions and longitudinal declines in FDG PET measurements of the regional cerebral metabolic rate for glucose (rCMRgl)[43,19,44,20,21,22,45,46,47,48,49,50,51], b) longitudinal declines in volumetric MRI measurements of whole brain shrinkage[52,53,54,45], c) PET measurements of the

magnitude and spatial extent of fibrillar amyloid burden[23], and d) cross-sectional and longitudinal measurements of the decline in long-term verbal memory[55,56,57,58,59,60,61,62]. Based on our findings, we have estimated the number of cognitively normal late-middle-aged *APOE ε4* homozygotes or heterozygotes needed to evaluate presymptomatic AD treatments using the FDG PET, volumetric MRI and cognitive endpoints, and we developed voxel-based image-analysis algorithms with improved power to detect and track AD while addressing the Type I error associated with multiple regional comparisons[36,63]. Meantime our amyloid PET findings suggest that fibrillar Aβ burden is "on the way up" in cognitively normal *APOE ε4* homozygotes and heterozygotes in their 50s and 60s (before fibrillar amyloid levels reaches the plateau observed in symptomatic patients[64]), that it will be possible to evaluate the differential effects of amyloid-modifying treatments in those carriers with more or less fibrillar Aβ (in case a presymptomatic treatment in normal people with significant Aβ burden is too little too late), and that it will be possible to assess the ability of these treatments to slow down further fibrillar Aβ deposition.

The Alzheimer's Prevention Initiative (API)

The API proposes to evaluate investigational amyloid-modifying treatments in healthy people who, based on their age and genetic background, are at the highest imminent risk of developing AD symptoms using brain imaging, cerebrospinal fluid (CSF), and cognitive endpoints[1]. This complements the newly established criteria for preclinical AD[2], as well as other presymptomatic/preclinical AD treatment trials proposed by the Dominantly Inherited Alzheimer's Network (DIAN)[65], the AD Cooperative Study (ADCS), and others[66,67].

The API has several goals: 1) to evaluate investigational AD-modifying treatments sooner than otherwise possible; 2) to determine the extent to which the treatment's effects on brain imaging and other biomarkers predicts a clinical benefit—information needed to help qualify biomarker endpoints for use in pivotal prevention trials; 3) to provide a better test of the amyloid hypothesis than clinical trials in symptomatic patients, when these treatments may be too little too late to exert their most profound effect; 4) to establish AD prevention registries needed to support these and other presymptomatic AD trials; and 5) to give those individuals at highest imminent risk of AD symptoms access to the most promising investigational treatments in clinical trials.

In one trial, we propose to study cognitively normal AD-causing *presenilin 1* [PS1] *E280A* mutation carriers, at least 35 years of age (i.e., within 10 years of the carriers' estimated median age at clinical onset), from the world's largest early-onset AD kindred, located in Antioquia, Colombia[1]. This extraordinary kindred, which has been followed for more than 20 years by Dr. Francisco Lopera and his colleagues, and includes about 5,000 people[68,69,70,71,72,73,74,75,76,77,78,33,79,80,81,82,83], with a sufficient number of presymptomatic carriers in the targeted age group to make it possible to relate a treatment's effects on both biomarker and clinical endpoints within 2–5 years. In the proposed trial, *PS1* mutation carriers would be randomized to active treatment or placebo, non-carriers would be assigned to placebo, and genetic test findings would not be disclosed to the family members simply because they are participating in this trial[84]. In the other trial, we propose to study cognitively normal 60–80 year-old *APOE ε4* homozygotes (and possibly heterozygotes), close to their estimated median age of clinical onset[1]. Including heterozygotes would depend on the safety and tolerability data for the chosen treatment, but would allow for both an increase in the available samples and an increase in the generalizablity of our findings[85,86].

For each subject group, we have proposed to conduct a 24 month double-blind, randomized, placebo-controlled trial using fibrillar amyloid PET, FDG PET, volumetric MRI, CSF, and cognitive endpoints[1]. Biological fluids and other MRI measurements would be used to permit exploratory studies. If after two years, the treatment is not associated with predicted effects on one or more of the biomarkers, the DSMB would declare futility, the trial would be discontinued, and the participants would be eligible to participate in a trial of the next most promising AD-modifying treatment. If, however, the treatment is associated with predicted biomarker effects, the trial would be continued to assess effects on our compound cognitive endpoint.

To support these and other presymptomatic AD trials, we plan to establish two AD prevention registries. We aim to enroll 2,000 members of the *PS1 E280A* kindred (along with DNA samples, *PS1 E280A* mutation testing and baseline cognitive assessments), about one-third of whom are projected to be mutation carriers, into the Colombian Registry by 2012. We aim to enroll several hundred thousand individuals in the US-based Alzheimer's Prevention Registry, some of whom will be invited to provide saliva samples for DNA acquisition and *APOE* screening. In anticipation of the Colombian trial, we have begun to acquire and analyze brain imaging and CSF samples in the *PS1* mutation carriers and non-carriers, a cyclotron/radiochemistry facility is being installed, and we have used data from the ongoing longitudinal study to estimate the sample sizes needed to detect a clinical effect using a composite cognitive endpoint.

While we believe that there is an opportunity to advance the evaluation of presymptomatic AD treatments, there is a responsibility to get it right. In October 2009, we hosted a meeting of 40 scientific advisors to get their input and help us to refine our proposal. In January 2010, we hosted a meeting with industry representatives to get their input and further refine our proposal[86]. In January 2011, we again met with industry representatives, academic advisors, and FDA and European Medicines Agency (EMA) officials, who provided thoughtful and encouraging feedback[85]. We have been communicating with pharmaceutical company leaders to explore their interest, the availability and timing of the most promising amyloid-modifying treatments, and to explore the scientific and logistical issues needed to prepare for our proposed trials. Selection of the drug will be made with the assistance of an independent academic advisory board, input from the affected kindred regarding potential benefits versus known adverse effects and previous use in human subjects, and will depend on factors such as target engagement, preclinical and clinical safety and tolerability data, dosing information, availability of the drug product, and in-kind industry support. We have proposed a mix of industry, philanthropic and federal funding, and we have indicated our intent to release the data to the public after the study is completed to help advance the use of biomarker and cognitive enrichment strategies and endpoints in future presymptomatic AD trials.

The proposed API treatment trials will help further develop the biomarker endpoints needed to evaluate a range of presymptomatic AD treatments, and will provide critically needed evidence to support the use of biomarker endpoints in the accelerated approval of presymptomatic AD treatments (i.e., to suggest that a treatment's biomarker effects may be reasonably likely to predict a clinical benefit in these or other populations). We believe that by helping to determine the extent to which the best established brain imaging and CSF biomarkers of AD budge in response to treatment, the extent to which they move in the predicted direction, and the extent to which the treatment's biomarker effects are associated with subsequent clinical benefit will help provide regulatory agencies the evidence they need to begin to consider approving presymptomatic treatments solely on biomarker endpoints in future trials. Moreover, these presymptomatic treatment trials will not only provide a better test of the amyloid hypothesis than clinical trials using the same treatment in

symptomatic AD patient, but will also provide research participants at the highest imminent risk of symptomatic AD access to the most promising and suitable investigational treatments sooner than otherwise possible.

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Reference List

1. Reiman EM, Langbaum JBS, Tariot PN. Alzheimer's Prevention Initiative: a proposal to evaluate presymptomatic treatments as quickly as possible. Biomarkers in Medicine. 2010; 4:3–14. [PubMed: 20383319]
2. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement. (in press).
3. Alzheimer's Association. 2011 Alzheimer's disease facts and figures. Alzheimer's & dementia: the journal of the Alzheimer's Association. 2011; 7:208–244.
4. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health. 1998; 88:1337–1342. [PubMed: 9736873]
5. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP. Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease: A Randomized Trial. JAMA: The Journal of the American Medical Association. 2008; 300:1027–1037. [PubMed: 18768414]
6. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol. 2002; 155:1081–1087. [PubMed: 12048221]
7. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, Stern Y. Physical activity, diet, and risk of Alzheimer disease. JAMA. 2009; 302:627–637. [PubMed: 19671904]
8. Haag MDM, Hofman A, Koudstaal PJ, Stricker BHC, Breteler MMB. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. Journal of Neurology, Neurosurgery, and Psychiatry. 2009; 80:13–17.
9. Peila R, White LR, Masaki K, Petrovitch H, Launer LJ. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. Stroke. 2006; 37:1165–1170. [PubMed: 16601212]
10. Szekely CA, Green RC, Breitner JCS, Ostbye T, Beiser AS, Corrada MM, Dodge HH, Ganguli M, Kawas CH, Kuller LH, Psaty BM, Resnick SM, Wolf PA, Zonderman AB, Welsh-Bohmer KA, Zandi PP. No advantage of Aβ42-lowering NSAIDs for prevention of Alzheimer dementia in six pooled cohort studies. Neurology. 2008; 70:2291–2298. [PubMed: 18509093]
11. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Welsh-Bohmer KA, Breitner JC. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol. 2004; 61:82–88. [PubMed: 14732624]
12. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL, Unverzagt FW, Willis SL. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA. 2002; 288:2271–2281. [PubMed: 12425704]
13. Kramp VP, Herrling P. List of drugs in development for neurodegenerative diseases: update June 2010. Neurodegener Dis. 2011; 8:44–94. [PubMed: 20689264]
14. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002; 297:353–356. [PubMed: 12130773]

15. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, Lopez OL, Burke G, Carlson MC, Fried LP, Kuller LH, Robbins JA, Tracy RP, Woolard NF, Dunn L, Snitz BE, Nahin RL, Furberg CD. for the Ginkgo Evaluation of Memory (GEM) Study Investigators. Ginkgo biloba for Prevention of Dementia: A Randomized Controlled Trial. JAMA. 2008; 300:2253–2262. [PubMed: 19017911]

16. ADAPT Research Group. Cognitive Function Over Time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): Results of a Randomized, Controlled Trial of Naproxen and Celecoxib. Archives of Neurology. 2008; 65:896–905. [PubMed: 18474729]

17. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN III, Assaf AR, Jackson RD, Kotchen JM, Wassertheil-Smoller S, Wactawski-Wende J. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003; 289:2651–2662. [PubMed: 12771112]

18. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004; 291:2947–2958. [PubMed: 15213206]

19. Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, Thibodeau SN, Osborne D. Preclinical evidence of Alzheimer's disease in persons homozygous for the ε4 allele for apolipoprotein E. N Engl J Med. 1996; 334:752–758. [PubMed: 8592548]

20. Reiman EM, Caselli RJ, Chen K, Alexander GE, Bandy D, Frost J. Declining brain activity in cognitively normal apolipoprotein E ε4 heterozygotes: A foundation for using positron emission tomography to efficiently test treatments to prevent Alzheimer's disease. Proc Natl Acad Sci USA. 2001; 98:3334–3339. [PubMed: 11248079]

21. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proc Natl Acad Sci USA. 2004; 101:284–289. [PubMed: 14688411]

22. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J. Correlations between apolipoprotein E ε4 gene dose and brain-imaging measurements of regional hypometabolism. Proc Natl Acad Sci USA. 2005; 102:8299–8302. [PubMed: 15932949]

23. Reiman EM, Chen K, Liu X, Bandy D, Yu M, Lee W, Ayutyanont N, Keppler J, Reeder SA, Langbaum JBS, Alexander GE, Klunk WE, Mathis CA, Price JC, Aizenstein HJ, DeKosky ST, Caselli RJ. Fibrillar amyloid-β burden in cognitively normal people at three levels of genetic risk for Alzheimer's disease. Proc Natl Acad Sci USA. 2009; 106:6820–6825. [PubMed: 19346482]

24. Reiman, EM.; Langbaum, JBS. Brain imaging in the evaluation of putative Alzheimer's disease slowing, risk-reducing and prevention therapies. In: Jagust, WJ.; D'Esposito, M., editors. Imaging the Aging Brain. Oxford University Press; New York: 2009. p. 319-350.

25. Fox NC, Warrington EK, Freeborough PA, Hartikainen P, Kennedy AM, Stevens JM, Rossor MN. Presymptomatic hippocampal atrophy in Alzheimer's disease. A longitudinal MRI study. Brain. 1996; 119:2001–2007. [PubMed: 9010004]

26. Mosconi L, Sorbi S, de Leon MJ, Li Y, Nacmias B, Myoung PS, Tsui W, Ginestroni A, Bessi V, Fayyazz M, Caffarra P, Pupi A. Hypometabolism exceeds atrophy in presymptomatic early-onset familial Alzheimer's disease. J Nucl Med. 2006; 47:1778–1786. [PubMed: 17079810]

27. Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW. Patterns of brain activation in people at risk for Alzheimer's disease. N Engl J Med. 2000; 343:450–456. [PubMed: 10944562]

28. Burggren AC, Zeineh MM, Ekstrom AD, Braskie MN, Thompson PM, Small GW, Bookheimer SY. Reduced cortical thickness in hippocampal subregions among cognitively normal apolipoprotein E e4 carriers. Neuroimage. 2008; 41:1177–1183. [PubMed: 18486492]

29. Small GW, Mazziotta JC, Collins MT, Baxter LR, Phelps ME, Mandelkern MA, Kaplan A, La Rue A, Adamson CF, Chang L. Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. JAMA. 1995; 273:942–947. [PubMed: 7884953]

30. Small GW, Ercoli LM, Silverman DH, Huang SC, Komo S, Bookheimer SY, Lavretsky H, Miller K, Siddarth P, Rasgon NL, Mazziotta JC, Saxena S, Wu HM, Mega MS, Cummings JL, Saunders AM, Pericak-Vance MA, Roses AD, Barrio JR, Phelps ME. Cerebral metabolic and cognitive

decline in persons at genetic risk for Alzheimer's disease. Proc Natl Acad Sci USA. 2000; 97:6037–6042. [PubMed: 10811879]

31. Small GW, Komo S, La RA, Saxena S, Phelps ME, Mazziotta JC, Saunders AM, Haines JL, Pericak-Vance MA, Roses AD. Early detection of Alzheimer's disease by combining apolipoprotein E and neuroimaging. Ann N Y Acad Sci. 1996; 802:70–78. [PubMed: 8993486]
32. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/β-amyloid42 ratio as a prediction of cognitive decline in nondemented older adults. Arch Neurol. 2007; 64:343–349. [PubMed: 17210801]
33. Johnson KA, Lopera F, Jones K, Becker A, Sperling R, Hilson J, Londono J, Siegert I, Arcos M, Moreno S, Madrigal L, Ossa J, Pineda N, Ardila A, Roselli M, Albert MS, Kosik KS, Rios A. Presenilin-1-associated abnormalities in regional cerebral perfusion. Neurology. 2001; 56:1545–1551. [PubMed: 11402113]
34. Valla J, Yaari R, Wolf AB, Kusne Y, Beach TG, Roher AE, Corneveaux JJ, Huentelman MJ, Caselli RJ, Reiman EM. Reduced posterior cingulate mitochondrial activity in expired young adult carriers of the APOE epsilon4 allele, the major late-onset Alzheimer's susceptibility gene. J Alzheimers Dis. 2010; 22:307–313. [PubMed: 20847408]
35. Beckett LA, Harvey DJ, Gamst A, Donohue M, Kornak J, Zhang H, Kuo JH. The Alzheimer's Disease Neuroimaging Initiative: Annual change in biomarkers and clinical outcomes. Alzheimers Dement. 2010; 6:257–264. [PubMed: 20451874]
36. Chen K, Langbaum JBS, Fleisher AS, Ayutyanont N, Reschke C, Lee W, Liu X, Bandy D, Alexander GE, Thompson PM, Foster NL, Harvey DJ, de Leon MJ, Koeppe RA, Jagust WJ, Weiner MW, Reiman EM. the Alzheimer's Disease Neuroimaging Initiative. Twelvemonth metabolic declines in probable Alzheimer's disease and amnestic mild cognitive impairment assessed using an empirically pre-defined statistical region-of-interest: Findings from the Alzheimer's Disease Neuroimaging Initiative. Neuroimage. 2010; 51:654–664. [PubMed: 20202480]
37. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med. 1989; 8:431–440. [PubMed: 2727467]
38. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med. 1996; 125:605–613. [PubMed: 8815760]
39. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001; 69:89–95. [PubMed: 11240971]
40. Katz R. Biomarkers and surrogate markers: an FDA perspective. NeuroRx. 2004; 1:189–195. [PubMed: 15717019]
41. Broich K. Outcome measures in clinical trials on medicinal products for the treatment of dementia: a European regulatory perspective. Int Psychogeriatr. 2007; 19:509–524. [PubMed: 17433121]
42. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261:921–923. [PubMed: 8346443]
43. Langbaum JB, Chen K, Caselli RJ, Lee W, Reschke C, Bandy D, Alexander GE, Burns CM, Kaszniak AW, Reeder SA, Corneveaux JJ, Allen AN, Pruzin J, Huentelman MJ, Fleisher AS, Reiman EM. Hypometabolism in Alzheimer-affected brain regions in cognitively healthy Latino individuals carrying the apolipoprotein E epsilon4 allele. Arch Neurol. 2010; 67:462–468. [PubMed: 20385913]
44. Reiman EM, Caselli RJ, Alexander GE, Chen K. Tracking the decline in cerebral glucose metablolism in persons and laboratory animals at genetic risk for Alzheimer's disease. Clinical Neuroscience Research. 2001; 1:194–206.
45. Chen K, Reiman EM, Alexander GE, Caselli RJ, Bandy D. Using partial-least squares to demonstrate a correlation between combined PET/MRI scores and apolipoprotein Eε4 gene dose. J Alz and Dementia. 2006; 2:S672–673.
46. Chen K, Reiman EM, Huan Z, Caselli RJ, Bandy D, Ayutyanont N, Alexander GE. Linking functional and structural brain images with multivariate network analyses: A novel application of the partial least square method. Neuroimage. 2009; 47:602–610. [PubMed: 19393744]

47. Corneveaux JJ, Liang WS, Reiman EM, Webster JA, Myers AJ, Zismann VL, Joshipura KD, Pearson JV, Hu-Lince D, Craig DW, Coon KD, Dunckley T, Bandy D, Lee W, Chen K, Beach TG, Mastroeni D, Grover A, Ravid R, Sando SB, Aasly JO, Heun R, Jessen F, Kolsch H, Rogers J, Hutton ML, Melquist S, Petersen RC, Alexander GE, Caselli RJ, Papassotiropoulos A, Stephan DA, Huentelman MJ. Evidence for an association between KIBRA and late-onset Alzheimer's disease. Neurobiol Aging. 2010; 31:901–909. [PubMed: 18789830]
48. Reiman EM, Webster JA, Myers AJ, Hardy J, Dunckley T, Zismann VL, Joshipura KD, Pearson JV, Hu-Lince D, Huentelman MJ, Craig DW, Coon KD, Liang WS, Herbert RH, Beach T, Rohrer KC, Zhao AS, Leung D, Bryden L, Marlowe L, Kaleem M, Mastroeni D, Grover A, Heward CB, Ravid R, Rogers J, Hutton ML, Melquist S, Petersen RC, Alexander GE, Caselli RJ, Kukull W, Papassotiropoulos A, Stephan DA. GAB2 alleles modify Alzheimer's risk in APOE ε4 carriers. Neuron. 2007; 54:713–720. [PubMed: 17553421]
49. Liang WS, Chen K, Lee W, Sidhar K, Corneveaux JJ, Allen AN, Myers A, Villa S, Meechoovet B, Pruzin J, Bandy D, Fleisher AS, Langbaum JB, Huentelman MJ, Jensen K, Dunckley T, Caselli RJ, Kaib S, Reiman EM. Association between GAB2 haplotype and higher glucose metabolism in Alzheimer's disease-affected brain regions in cognitively normal APOEepsilon4 carriers. Neuroimage. 2011; 54:1896–1902. [PubMed: 20888920]
50. Reiman EM, Chen K, Caselli RJ, Alexander GE, Bandy D, Adamson JL, Lee W, Cannon A, Stephan EA, Stephan DA, Papassotiropoulos A. Cholesterol-Related Genetic Risk Scores are Associated with Hypometabolism in Alzheimer's-Affected Brain Regions. Neuroimage. 2008; 40:1214–1221. [PubMed: 18280754]
51. Reiman EM, Chen K, Langbaum JB, Lee W, Reschke C, Bandy D, Alexander GE, Caselli RJ. Higher serum total cholesterol levels in late middle age are associated with glucose hypometabolism in brain regions affected by Alzheimer's disease and normal aging. Neuroimage. 2010; 49:169–176. [PubMed: 19631758]
52. Alexander GE, Chen K, Reiman EM, Caselli RJ, Lewis D, Bandy D, Prouty A. Longitudinal declines of gray matter in cognitively normal apolopoprotein E ε4 homozygotes and heterozygotes evaluated by voxel-based MRI morphometry. Neurobiol Aging. 2002:s363.
53. Chen K, Reiman EM, Alexander GE, Caselli RJ, Gerkin R, Bandy D, Domb A, Osborne D, Fox N, Crum WR, Saunders AM, Hardy J. Correlations between apolipoprotein E ε4 gene dose and whole brain atrophy rates. Am J Psychiatry. 2007; 164:916–921. [PubMed: 17541051]
54. Chen K, Reiman EM, Alexander GE, Bandy D, Renaut R, Crum WR, Fox NC, Rossor MN. An automated algorithm for the computation of brain volume change from sequential MRIs using an iterative principal component analysis and its evaluation for the assessment of whole-brain atrophy rates in patients with probable Alzheimer's disease. Neuroimage. 2004; 22:134–143. [PubMed: 15110003]
55. Caselli RJ, Hentz JG, Osborne D, Snyder CH, Alexander GE, Reiman EM. Presymptomatic longitudinal decline in frontally mediated cognitive skills and memory in cognitively normal late middle aged APOE e4 carriers. Alzheimer's and Dementia. 2006; 2:S292.
56. Caselli RJ, Reiman EM, Osborne D, Hentz JG, Baxter LC, Hernandez JL, Alexander GG. Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE ε4 allele. Neurology. 2004; 62:1990–1995. [PubMed: 15184602]
57. Caselli RJ, Osborne D, Reiman EM, Hentz JG, Barbieri CJ, Saunders AM, Hardy J, Graff-Radford NR, Hall GR, Alexander GE. Preclinical cognitive decline in late middle-aged asymptomatic apolipoprotein E-ε4/4 homozygotes: a replication study. J Neurol Sci. 2001; 189:93–98. [PubMed: 11535238]
58. Caselli RJ, Graff-Radford NR, Reiman EM, Weaver A, Osborne D, Lucas J, Uecker A, Thibodeau SN. Preclinical memory decline in cognitively normal apolipoprotein E-ε4 homozygotes. Neurology. 1999; 53:201–207. [PubMed: 10408560]
59. Caselli RJ, Reiman EM, Locke DE, Hutton ML, Hentz JG, Hoffman-Snyder C, Woodruff BK, Alexander GE, Osborne D. Cognitive domain decline in healthy Apolipoprotein E ε4 homozygotes before the diagnosis of Mild Cognitive Impairment. Arch Neurol. 2007; 64:1306–1311. [PubMed: 17846270]

60. Caselli RJ, Chen K, Lee W, Alexander GE, Reiman EM. Correlating Cerebral Hypometabolism With Future Memory Decline in Subsequent Converters to Amnestic Pre-Mild Cognitive Impairment. Archives of Neurology. 2008; 65:1231–1236. [PubMed: 18779428]
61. Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, Baxter LC, Rapcsak SZ, Shi J, Woodruff BK, Locke DEC, Hoffman-Snyder C, Alexander GE, Rademakers R, Reiman EM. Longitudinal modeling of age-related memory decline and the APOE ε4 effect. N Engl J Med. 2009; 361:255–263. [PubMed: 19605830]
62. Caselli RJ, Dueck AC, Locke DE, Sabbagh MN, Ahern GL, Rapcsak SZ, Baxter LC, Yaari R, Woodruff BK, Hoffman-Snyder C, Rademakers R, Findley S, Reiman EM. Cerebrovascular risk factors and preclinical memory decline in healthy APOE ε4 homozgyotes. Neurology. 2011; 76:1078–1084. [PubMed: 21325652]
63. Chen K, Ayutyanont N, Langbaum JBS, Fleisher AS, Reschke C, Lee W, Liu X, Bandy D, Alexander GE, Thompson PM, Shaw L, Trojanowki JQ, Jack CR Jr, Landau SM, Foster NL, Harvey DJ, Weiner MW, Koeppe RA, Jagust WJ, Reiman EM. Alzheimer's Disease Neuroimaging Initiative. Characterizing Alzheimer's disease using a hypometabolic convergence index. Neuroimage. (submitted).
64. Klunk WE, Mathis CA, Price JC, Lopresti BJ, DeKosky ST. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain. 2006; 129:2805–2807. [PubMed: 17071918]
65. Bateman RJ, Aisen PS, De Strooper B, Fox NC, Lemere CA, Ringman JM, Salloway S, Sperling RA, Windisch M, Xiong C. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. Alzheimers Res Ther. 2011; 2:35.
66. Aisen PS, Andrieu S, Sampaio C, Carrillo M, Khachaturian ZS, Dubois B, Feldman HH, Petersen RC, Siemers E, Doody RS, Hendrix SB, Grundman M, Schneider LS, Schindler RJ, Salmon E, Potter WZ, Thomas RG, Salmon D, Donohue M, Bednar MM, Touchon J, Vellas B. Report of the task force on designing clinical trials in early (predementia) AD. Neurology. 2011; 76:280–286. [PubMed: 21178097]
67. Khachaturian ZS, Barnes D, Einstein R, Johnson S, Lee V, Roses A, Sager MA, Shankle WR, Snyder PJ, Petersen RC, Schellenberg G, Trojanowski J, Aisen P, Albert MS, Breitner JCS, Buckholtz N, Carrillo M, Ferris S, Greenberg BD, Grundman M, Khachaturian AS, Kuller LH, Lopez OL, Maruff P, Mohs RC, Morrison-Bogorad M, Phelps C, Reiman E, Sabbagh M, Sano M, Schneider LS, Siemers E, Tariot P, Touchon J, Vellas B, Bain LJ. Developing a national strategy to prevent dementia: Leon Thal Symposium 2009. Alzheimer's and Dementia. 2010; 6:89–97.
68. Acosta-Baena N, Sepulveda-Falla D, Lopera-Gomez CM, Jaramillo-Elorza MC, Moreno S, Aguirre-Acevedo DC, Saldarriaga A, Lopera F. Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. Lancet Neurol. 2011; 10:213–220. [PubMed: 21296022]
69. Arango-Lasprilla JC, Cuetos F, Valencia C, Uribe C, Lopera F. Cognitive changes in the preclinical phase of familial Alzheimer's disease. J Clin Exp Neuropsychol. 2007; 29:892–900. [PubMed: 17852592]
70. Arango Lasprilla JC, Iglesias J, Lopera F. Neuropsychological study of familial Alzheimer's disease caused by mutation E280A in the presenilin 1 gene. Am J Alzheimers Dis Other Demen. 2003; 18:137–146. [PubMed: 12811988]
71. Ardila A, Lopera F, Rosselli M, Moreno S, Madrigal L, Arango-Lasprilla JC, Arcos M, Murcia C, Arango-Viana JC, Ossa J, Goate A, Kosik KS. Neuropsychological profile of a large kindred with familial Alzheimer's disease caused by the E280A single presenilin-1 mutation. Arch Clin Neuropsychol. 2000; 15:515–528. [PubMed: 14590205]
72. Lopera F, Ardilla A, Martinez A, Madrigal L, Arango-Viana JC, Lemere CA, Arango-Lasprilla JC, Hincapie L, Arcos-Burgos M, Ossa JE, Behrens IM, Norton J, Lendon C, Goate AM, Ruiz-Linares A, Rosselli M, Kosik KS. Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation. JAMA. 1997; 277:793–799. [PubMed: 9052708]
73. Rosselli MC, Ardila AC, Moreno SC, Standish VC, Arango-Lasprilla JC, Tirado VM, Ossa JM, Goate AM, Kosik KS, Lopera F. Cognitive decline in patients with familial Alzheimer's disease associated with E280a presenilin-1 mutation: a longitudinal study. J Clin Exp Neuropsychol. 2000; 22:483–495. [PubMed: 10923058]

74. Quiroz YT, Budson AE, Celone K, Ruiz A, Newmark R, Castrillon G, Lopera F, Stern CE. Hippocampal hyperactivation in presymptomatic familial Alzheimer's disease. Ann Neurol. 2010; 68:865–875. [PubMed: 21194156]

75. Bobes MA, Garcia YF, Lopera F, Quiroz YT, Galan L, Vega M, Trujillo N, Valdes-Sosa M, Valdes-Sosa P. ERP generator anomalies in presymptomatic carriers of the Alzheimer's disease E280A PS-1 mutation. Hum Brain Mapp. 2010; 31:247–265. [PubMed: 19650138]

76. Cuetos F, Arango-Lasprilla JC, Uribe C, Valencia C, Lopera F. Linguistic changes in verbal expression: a preclinical marker of Alzheimer's disease. J Int Neuropsychol Soc. 2007; 13:433–439. [PubMed: 17445292]

77. Dorfman VB, Pasquini L, Riudavets M, Lopez-Costa JJ, Villegas A, Troncoso JC, Lopera F, Castano EM, Morelli L. Differential cerebral deposition of IDE and NEP in sporadic and familial Alzheimer's disease. Neurobiol Aging. 2010; 31:1743–1757. [PubMed: 19019493]

78. Gomez-Isla T, Growdon WB, McNamara MJ, Nochlin D, Bird TD, Arango JC, Lopera F, Kosik KS, Lantos PL, Cairns NJ, Hyman BT. The impact of different presenilin 1 andpresenilin 2 mutations on amyloid deposition, neurofibrillary changes and neuronal loss in the familial Alzheimer's disease brain: evidence for other phenotype-modifying factors. Brain. 1999; 122 (Pt 9):1709–1719. [PubMed: 10468510]

79. Lemere CA, Lopera F, Kosik KS, Lendon CL, Ossa J, Saido TC, Yamaguchi H, Ruiz A, Martinez A, Madrigal L, Hincapie L, Arango JC, Anthony DC, Koo EH, Goate AM, Selkoe DJ, Arango JC. The E280A presenilin 1 Alzheimer mutation produces increased A beta 42 deposition and severe cerebellar pathology. Nat Med. 1996; 2:1146–1150. [PubMed: 8837617]

80. Lendon CL, Martinez A, Behrens IM, Kosik KS, Madrigal L, Norton J, Neuman R, Myers A, Busfield F, Wragg M, Arcos M, Arango Viana JC, Ossa J, Ruiz A, Goate AM, Lopera F. E280A PS-1 mutation causes Alzheimer's disease but age of onset is not modified by ApoE alleles. Hum Mutat. 1997; 10:186–195. [PubMed: 9298817]

81. Mejia S, Giraldo M, Pineda D, Ardila A, Lopera F. Nongenetic factors as modifiers of the age of onset of familial Alzheimer's disease. Int Psychogeriatr. 2003; 15:337–349. [PubMed: 15000414]

82. Parra MA, Sala SD, Abrahams S, Logie RH, Mendez LG, Lopera F. Specific deficit of colour-colour short-term memory binding in sporadic and familial Alzheimer's disease. Neuropsychologia. 2011

83. Parra MA, Abrahams S, Logie RH, Mendez LG, Lopera F, Della SS. Visual short-term memory binding deficits in familial Alzheimer's disease. Brain. 2010; 133:2702–2713. [PubMed: 20624814]

84. Kosik KS, Lopera F. Genetic testing must recognize impact of bad news on recipient. Nature. 2008; 454:158–159. [PubMed: 18615057]

85. Strobel, G. [Accessed March 15 2011] Alzheimer's Prevention Intiative: a six part series. Alzheimer Research Forum. 2011. http://www.alzforum.org/new/detail.asp?id=2720

86. Strobel, G. [Accessed February 25, 2010] Phoenix: Vision of shared prevention trials lures pharma to table. Alzheimer Research Forum. 2010. http://www.alzforum.org/new/detail.asp?id=2374