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Alzheimer's Prevention Initiative: a proposal to evaluate presymptomatic treatments as quickly as possible

Eric M Reiman^{1,2,3,4,5,†}, Jessica BS Langbaum^{1,2,5}, and Pierre N Tariot^{1,2,5,6}

¹The Banner Alzheimer's Institute, 901 E. Willetta St., Phoenix, AZ 85006, USA

²Banner Health Research, Sun City, AZ, USA

³The University of Arizona, Tucson, AZ, USA

⁴The Translational Genomics Research Institute, Phoenix, AZ, USA

⁵The Arizona Alzheimer's Consortium, Phoenix, AZ, USA

⁶The Alzheimer's Disease Cooperative Study

Abstract

Now is the time to launch the era of Alzheimer's disease (AD) prevention research, establish the methods and infrastructure to rapidly evaluate presymptomatic AD treatments and evaluate them rigorously and rapidly in randomized clinical trials. This article is a call to arms. It contends that the evaluation of presymptomatic AD treatments must become an urgent priority, it identifies what is holding us back and proposes new public policies and scientific strategies to overcome these roadblocks. It defines the term 'presymptomatic AD treatment,' notes the best established biomarkers of AD progression and pathology and suggests how they could be used to rapidly evaluate presymptomatic AD treatments in the people at risk. It introduces an approach to evaluate presymptomatic AD treatments in asymptomatic people at the highest risk of imminent clinical onset and determines the extent to which the treatment's biomarker predicts a clinical outcome. We propose an Alzheimer's Prevention Initiative, which is now being reviewed and refined in partnership with leading academic and industry investigators. It is intended to evaluate the most promising presymptomatic AD treatments, help develop a regulatory pathway for their accelerated approval using reasonably likely surrogate end points and find demonstrably effective presymptomatic AD treatments as quickly as possible.

Keywords

amyloid; apolipoprotein; biomarker; clinical trial; genetics; MRI; PET; presenilin; public policy; surrogate marker

Alzheimer's disease (AD) is an unacceptable problem. It takes a catastrophic toll on patients and family caregivers, and it is projected to have a financially overwhelming effect around the world in our children's lifetime. In our opinion, the greatest roadblock in the scientific fight against AD is not necessarily the discovery of new treatments, but the means to evaluate them

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† Author for correspondence: Tel.: +1 602 839 6999 Fax: +1 602 839 6523 eric.reiman@ bannerhealth.com .

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presymptomatically, when they may have their greatest impact, in a sufficiently rapid and rigorous way. It currently takes too many cognitively normal research subjects, too many years and too much money to evaluate more than a few presymptomatic AD treatments using clinical end points. Brain imaging and other biomarkers of AD progression and pathology have the potential to accelerate the evaluation of presymptomatic AD treatments. However, regulatory agencies are unlikely to provide accelerated approval for a presymptomatic AD treatment based solely on biomarker end points, without additional evidence from randomized clinical trials (RCTs) to conclude that a treatment's biomarker effects are reasonably likely to predict a clinical benefit. In the meantime, sponsors are reluctant to conduct presymptomatic AD trials without a regulatory approval pathway. This dilemma may at first seem like an insurmountable 'catch-22', leading to a sense of nihilism and a lack of urgency, but inaction is not an option. Given both the extraordinary stakes and opportunity now at hand, we are convinced that now is the time to launch the public policy and scientific initiatives needed to accelerate the evaluation of presymptomatic AD treatments.

Anticipating the presymptomatic treatment & diagnosis of AD

To begin, we define 'presymptomatic AD treatments' as "those interventions that are initiated before apparent cognitive decline and intended to reduce the chance of developing AD-related symptoms." The term is introduced for two reasons:

- To help address uncertainties related to the use of the terms primary versus secondary prevention, including their relationship to presymptomatic or symptomatic evidence of AD at the time a treatment is started;
- We anticipate that regulatory agencies will find it easier to consider a 'presymptomatic AD treatment' indication than an 'AD prevention' indication (at least until there is compelling evidence that a treatment can avert symptomatic AD throughout a person's lifetime). The proposed term would be used whether a presymptomatic treatment 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 further divide these presymptomatic AD treatments into those that exert their beneficial effects by compensating for the underlying disease and those that exert their beneficial effects by directly or indirectly reversing or slowing down the progression of the underlying disease. We anticipate the eventual need to specify whether a presymptomatic AD treatment is initiated before or after presymptomatic biomarker evidence of disease, since this subclassification may predict a differential response to treatment and it may or may not require the treatment to be associated with an accompanying diagnostic test. Although the diagnosis of AD currently requires symptomatic evidence of the disease, the concept of a presymptomatic AD-modifying treatment anticipates the time when AD is defined on the basis of biological criteria, and related to the presymptomatic and progressively symptomatic stages of the disorder.

While we would recommend using the term 'presymptomatic AD trial' in place of 'AD prevention trial' in professional communications, the latter term may be more readily understood by the general public. It underscores the ultimate goal in the scientific fight against AD and it does not dismiss the possibility that some of the treatments now in development might have the chance to prevent symptomatic AD completely. For instance, if the amyloid- β ($A\beta$) peptide plays a critical role in the final common pathway associated with the predisposition to AD, and if a treatment now in development targets the right form of $A\beta$ and is started sufficiently early, it may be possible to prevent symptomatic AD completely. For these reasons, we use the term 'Alzheimer's Prevention Initiative' to describe the scientific strategy and public policies described below, and which continues to be refined in partnership with leading academic and industry investigators and other stakeholders.

Presymptomatic AD trials: why now?

There are several compelling reasons to accelerate the evaluation of presymptomatic AD treatments starting now, as described in the following sections.

Demonstrably effective presymptomatic AD treatments are urgently needed to avert an overwhelming crisis

Alzheimer's disease is the most common form of disabling cognitive impairment in older people, afflicting approximately one tenth of people older than 65 years of age and almost half of those older than 85 [1]. With the skyrocketing number of people living to older ages, the financial toll of AD is projected to become overwhelming by the time today's young adults become senior citizens [2,3]. According to a recent report [101], more than 35 million people are afflicted by AD and other dementias; this number is estimated to nearly double every 20 years, to more than 65 million in 2030 and more than 115 million in 2050, and there are likely to be an even greater number of people in the earlier symptomatic stages of AD.

Promising treatments to reduce the risk of symptomatic AD are ready to be evaluated in RCTs

With the quickening pace of scientific discoveries, researchers continue to add to the list of currently available, sufficiently safe and well-tolerated interventions, suggested but not yet proven to postpone the onset and reduce the risk of symptomatic AD. Interventions proposed to reduce the risk of symptomatic AD include a variety of currently available healthy lifestyle [4,5] and dietary interventions [6], medications approved for other indications [7-9] and dietary supplements [10]. A treatment that delayed the onset of symptomatic AD by only 5 years without increasing longevity would potentially reduce the number of patients by half [2], illustrating the impact that a symptomatic AD-postponing treatment could have on this rapidly growing public health problem.

A rapidly growing number of investigational AD-modifying treatments are now being studied in symptomatic AD RCTs

The list includes numerous A β -modifying medication and immunization treatments, a much smaller number of tau-modifying and microtubule-stabilizing treatments, and treatments suggested to target other elements of the postulated pathogenic cascade [11]. If any one of these treatments is targeting critical pathogenic events, is sufficiently safe and well tolerated, and is introduced early enough, it could have an enormous public health benefit. There will soon be enough safety and tolerability data to permit the evaluation of some of these treatments in asymptomatic people at increased risk for symptomatic AD.

Several otherwise promising treatments may be most effective if started before the onset of symptoms

It has been suggested that certain A β -modifying treatments may be most effective if started before the appearance of both fibrillar A β and neurofibrillary neuropathology. There is a compelling reason to evaluate promising treatments presymptomatically, whether or not they significantly slow down the clinical course in symptomatic patients, as long as the treatment is considered sufficiently safe and well tolerated. While there is a growing concern that investigational AD-modifying treatments now in RCTs may offer too little help too late to exert a profound effect even in patients in the mildest symptomatic stages of AD, we and others hold onto the hope that symptomatic AD patients may still have at least some therapeutic response to these treatments, we postulate that symptomatic AD patients may benefit from a combination of treatments that target early and late stages of the disease (e.g., a combination of A β - and tau-modifying therapies), and we wish to emphasize the importance of doing everything in our power to address the needs of our symptomatic AD patients and families. To

be clear, the accelerated evaluation of presymptomatic AD patients should not come at the expense of our patients.

Investigational treatments may not be ready for evaluation in most cognitively normal people until more safety & tolerability data are acquired in clinically affected patients, they may be ready sooner in those who for genetic or other reasons are at the highest imminent risk of symptomatic AD

Cognitively normal people at unusually high imminent risk of symptomatic AD include carriers of relatively rare early-onset AD-causing *PS1* [12], *PS2* [13] and *APP* [14] mutations close to their family's estimated median age at clinical onset, people with two copies of the *APOE* $\epsilon 4$ allele, a late-onset AD susceptibility gene [15], close to their estimated median age at clinical onset and, according to initial studies, older people with a cerebrospinal fluid (CSF) biomarker profile characterized by high total (t)- or phospho (p)-tau and low $A\beta_{42}$ levels [16,17].

Researchers have developed several promising imaging & CSF biomarkers to detect or track the brain changes associated with the predisposition to AD

While researchers continue to investigate a number of different brain imaging, biological fluid and other biomarker measurements for use in the early detection and tracking of AD (see references [18-22], for example), to date the best established biomarkers of AD progression and pathology include reduced fluorodeoxyglucose (FDG) PET measurements of the cerebral metabolic rate for glucose (CMRgl) in brain regions preferentially affected by AD (Figure 1A) [23-25]; structural MRI measurements of brain shrinkage (i.e., hippocampal, entorhinal cortex and whole brain volume loss, ventricular enlargement and gray matter loss and cortical thinning in regions preferentially affected by AD (Figure 1B)) [26-28]; PET measurements of fibrillar $A\beta$ burden (using ^{11}C -labeled Pittsburgh Compound-B (Figure 1C) or ^{11}C - or ^{18}F -labeled ligands now in development) [29-37] and certain CSF analytes (i.e., low CSF $A\beta_{42}$ levels, high t- or p-tau levels, or a combination of low $A\beta_{42}$ and high t-tau or p-tau levels) [16,17,38,39].

Several of these imaging and CSF biomarkers have shown value in the presymptomatic detection and tracking of AD. For instance, we and our colleagues have used imaging techniques in cognitively normal initially late-middle-aged *APOE* $\epsilon 4$ homozygotes, heterozygotes and noncarriers to detect or track CMRgl reductions (Figure 2), whole brain shrinkage (Figure 3), and higher fibrillar $A\beta$ burden (Figure 4) associated with an increased genetic risk for AD (Figures 2-4). These studies suggest how the imaging techniques could be used to evaluate presymptomatic AD treatments in a few hundred cognitively normal late-middle-aged *APOE* $\epsilon 4$ homozygotes or heterozygotes in 2-year proof-of-concept RCTs [26, 27,31,40-46] and complement the work of other researchers [30,47-58]. Researchers have also used imaging techniques to show CMRgl declines, whole brain shrinkage and increased fibrillar $A\beta$ burden in cognitively normal carriers of early-onset AD-causing mutations (Figure 5) [35,59-71], and to demonstrate that fibrillar $A\beta$ burden in cognitively normal older adults is associated with subsequent rates of progression to symptomatic AD [34]. Moreover, they have reported low $A\beta_{42}$ levels and high t-tau and p-tau levels in cognitively normal *APOE* $\epsilon 4$ carriers [72,73], and that the combination of high t-tau or p-tau levels and low $A\beta_{42}$ levels predicts subsequent rates of progression from cognitive normality to the early symptomatic stages of AD [16,17,74]. These presymptomatic AD biomarkers could be used to rapidly evaluate presymptomatic AD treatments in *APOE* $\epsilon 4$ carriers, early-onset AD-causing mutation carriers or research participants with presymptomatic biomarker evidence of AD in proof-of-concept RCTs.

What is holding us back?

Despite the urgent need to evaluate promising presymptomatic treatments for AD and the scientific opportunities now at hand, several roadblocks continue to hold us back. These are discussed in the following sections.

It takes too many people, too much money & too many years to conduct adequately powered presymptomatic AD RCTs using clinical end points

As noted previously, it takes too many cognitively normal people and too much time to find demonstrably effective presymptomatic AD treatments using clinical end points, such that enough people develop the clinical end points needed to distinguish between active treatment and placebo groups with adequate statistical power. Although a small number of presymptomatic AD RCTs have been performed [75-78], they have required thousands of subjects, many years of treatment and restriction of the sample to older adults in order to achieve sufficient statistical power. If we continue to rely on the use of clinical end points in presymptomatic AD RCTs, we will not be able to evaluate the range of promising presymptomatic treatments or those treatments started in middle age, when several treatments (e.g., hormone-replacement, cholesterol-lowering and blood pressure-lowering therapies) have been postulated to have their most significant therapeutic effects. Pharmaceutical and biotechnological companies are reluctant to sponsor prevention trials that take longer than their duration of marketing exclusivity, and the government may be reluctant to support many presymptomatic AD trials at the same time, given their extraordinary expense. Therefore, given the stakes, “who in his right mind would consider studying just one of these [presymptomatic AD] treatments at a time?” [GINGRICH N, ALZHEIMER'S STUDY GROUP, PERS. COMM.].

Regulatory agencies will not approve a presymptomatic AD treatment based solely on biomarker end points

Brain imaging and CSF biomarker methods could be used in *APOE ε4* carriers and other at-risk subjects to evaluate presymptomatic AD treatments in RCTs. Still, these studies will not provide a sufficient path for the accelerated regulatory agency approval of presymptomatic treatments until RCTs provide sufficient evidence to conclude that a treatment's effect on these biomarker end points is reasonably likely to predict a clinical benefit [26,79,80]. In the next section, we propose a strategy to address this critical need.

For now, some humility is needed when it comes to a reliance on these biomarkers in RCTs. It is not yet known how much a given biomarker will budge in response to different treatments. Similarly, it is not known whether the treatment might have a confounding effect on the biomarker unrelated to AD progression (e.g., a change in brain swelling, synaptic activity, glucose metabolism or arborization or analyte turnover), as illustrated in the RCT of the first active Aβ immunization therapy [81]. Finally, researchers still do not know the extent to which the biomarker effects of different AD-modifying treatments, alone or in combination, will predict a clinical benefit. While the only way to answer these questions is to characterize and compare each of the promising biomarkers in clinical trials, this surrogate marker development effort introduces significant cost and complexity, and it is typically not the primary focus of sponsors seeking to evaluate a particular drug product in the most cost-effective way.

We currently lack the public policies needed to accelerate the evaluation of presymptomatic AD treatments

As previously noted, there has been little financial incentive for companies to conduct time-consuming and expensive presymptomatic AD RCTs; there has been little financial incentive to investigate off-patent treatments, including health-promoting lifestyle interventions, and there has been little short-term financial incentive to include multiple expensive brain imaging

and other biomarker measurements in RCTs to help determine which biomarker is mostly likely to predict a treatment's therapeutic effect. It is time to make this effort an urgent priority. Given the stakes, it is time for federal governments to play a leadership role in this critically important endeavor.

The Alzheimer's Study Group [102], Leaders Engaged on AD (LEAD), the Alzheimer's Association, Act-AD, Prevent Alzheimer's Disease 2020 and other stakeholders [82-85] have proposed new public policies to help transform AD research and care. Here, we propose a strategically focused Alzheimer's Prevention Initiative, which consists of new scientific strategies, public policies and the sense of urgency needed to launch an era of AD prevention research and find demonstrably effective presymptomatic AD treatments as soon as possible [26]. In our opinion, it is not only important to launch an initiative like this, but to do so in a way that maximizes the chance for success. This will entail extensive collaboration with scientific, industry and public partners, capitalizing on the successes and lessons of other collaborative efforts such as the Alzheimer's Disease Cooperative Study (ADCS), Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Dominantly Inherited Alzheimer's Network (DIAN). Success will be measured, to some degree, by the extent to which a new initiative such as this can leverage and complement the goals and aims of other related programs, as well as the strengths of individual investigators and advisors. Transparency and accountability will be critical, along with the imperative to assure that the many ethical issues that will arise are handled as thoughtfully as possible.

A new scientific paradigm

Despite the roadblocks discussed previously, we remain optimistic regarding the ability to evaluate presymptomatic AD treatments. These suggestions are discussed in the following sections.

Evaluate the most promising presymptomatic AD treatments in cognitively normal participants in surrogate marker development/presymptomatic AD treatment RCTs

We propose to evaluate promising A β -modifying treatments using clinical, cognitive and multiple biomarker end points in asymptomatic early-onset AD-causing mutation carriers, *APOE* ϵ 4 homozygotes close to their estimated median age at clinical onset and older adults with a high-risk CSF biomarker signature [16,17,74] in 60-month RCTs using fibrillar A β PET, FDG PET, structural MRI, CSF and cognitive measurements, as well as clinical end points. If the Data Safety Monitoring Board (DSMB) found no promising biomarker or clinical effects during the course of the study (i.e., no evidence that the active treatment was associated with the predicted effects on measurements of A β or tau pathology, regional CMRgl decline, brain shrinkage, long-term memory or clinical ratings), it could declare futility, thereby giving those people at the highest imminent risk for symptomatic AD access to other investigational treatments in presymptomatic therapeutic trials while conserving precious resources. If instead, the DSMB found promising biomarker or clinical effects, the study would continue using biomarker, cognitive and clinical end points.

This presymptomatic AD treatment trial/surrogate marker development paradigm would make it possible to evaluate investigational presymptomatic treatments trials sooner than otherwise possible (i.e., with safety and tolerability data from fewer patients), since it would provide the data needed to show the extent to which an established treatment's effects on different biomarkers predicts a clinical benefit. This paradigm would provide some of the evidence needed to approve presymptomatic treatments solely on the basis of reasonably likely surrogate end points in future prevention trials, and would help trial sponsors select the most suitable biomarker end points for these trials. We postulate that the combined effects of an amyloid-modifying treatment on measures of A β pathology and one or more theoretically downstream

measurements (i.e., regional CMRgl decline, whole brain shrinkage, t-tau or p-tau increases and/or long-term memory decline) predict subsequent rates of conversion to symptomatic AD onset (e.g., a Clinical Dementia Rating [86] global score >0). If the treatment was not associated with a clinical benefit, this paradigm would raise new questions about the amyloid hypothesis and A β -modifying treatments, accelerating the investigation of AD mechanisms and treatments unrelated to A β .

Embed multiple biomarkers in clinical trials of promising AD-slowing treatments & determine the extent to which markers of AD progression & pathology predict clinical outcome

Longitudinal studies such as the ADNI [46], the recently initiated DIAN and our study of initially late-middle-aged cognitively normal *APOE* ϵ 4 homozygotes, heterozygotes and noncarriers [27,31,40,41,43,46] include a range of promising brain imaging biomarker measurements of AD progression and pathology. Clinical trials of promising AD-slowing treatments should also include multiple biomarkers, not just to secure regulatory approval for the intervention under study, but to help establish surrogate end points for future prevention trials. As suggested below, federal governments could provide the tax incentives or public-private partnership funding needed to validate surrogate end points as quickly as possible. The use of multiple biomarkers would help to overcome the possibility of imaging modality-specific confounding treatment effects, for example, the modality-specific effects of an A β -modifying treatment on MRI measurements of whole-brain volume unrelated to the treatment's effects on neuronal loss or the modality-specific effects of treatment on FDG PET measurements of CMRgl unrelated to synaptic loss. In hindsight, for instance, it would have been beneficial to have included FDG PET measurements to evaluate an effect of the first active A β immunization therapy on disease progression in light of the treatment's unanticipated effects on MRI measurements of brain volume [81].

Establish the infrastructure needed to conduct multiple presymptomatic AD RCTs simultaneously

This infrastructure would include national registries of potentially interested, cognitively normal people for both proof-of-concept and pivotal presymptomatic AD trials, along with the means to ascertain genetic, brain imaging and other biomarker indicators of AD risk in these RCTs.

Public policy recommendations

Apart from new scientific strategies, new public policies are needed to accelerate the evaluation of presymptomatic AD treatments. We will discuss our recommendations in the following sections.

Give pharmaceutical companies a compelling financial incentive to evaluate presymptomatic AD treatments

The extension of marketing exclusivity has promoted the development of orphan drugs for rare disorders. Offering extended marketing exclusivity for demonstrably effective presymptomatic AD treatments, perhaps starting the time-clock with completion of the expensive, large and time-consuming pivotal prevention trials, would galvanize the evaluation of promising presymptomatic treatments, and it could help avert a financially overwhelming crisis.

Provide federal funding to evaluate presymptomatic AD treatments

Treatments without a sufficient marketing incentive, such as currently available medications with limited or no patent coverage, dietary supplements and health-promoting lifestyle

interventions that have been suggested to reduce the risk of AD, could be funded with federal support.

Provide federal funding or tax credits for the inclusion of multiple complementary brain imaging & other biomarker measurements in RCTs of promising AD-slowing treatments & require pharmaceutical companies to make the data publicly available after the trials are completed

This policy would accelerate the development of reasonably likely surrogate end points for the evaluation of promising AD-slowing treatments, and it would provide a path for the accelerated regulatory agency approval of presymptomatic treatments.

Create public–private partnerships

It is important that public–private partnerships that are needed to evaluate promising presymptomatic treatments are created, and surrogate markers are developed in the most rapid and rigorous way. This partnership would include academia, industry, federal and regulatory agencies, and other important stakeholders.

Conclusion

Now is the time to make the scientific understanding and prevention of AD a national priority. The Alzheimer’s Prevention Initiative needs to be established with a sense of urgency, public policies and research infrastructure put in place, and presymptomatic AD treatment/surrogate marker development RCTs planned in order to launch an era of AD prevention research to find demonstrably effective risk-reducing and prevention therapies, and avert an overwhelming crisis. Leading academic and industry researchers, policymakers and other stakeholders need to be brought together in order to accomplish the goals set forth in the most appropriate, inclusive and effective way. Let us find demonstrably effective presymptomatic AD treatments without losing a generation.

Executive summary

Presymptomatic Alzheimer’s disease treatments: a proposed definition

- A proposed definition of presymptomatic Alzheimer’s disease (AD) treatment is: “those interventions that are initiated before apparent cognitive decline and intended to reduce the chance of developing AD-related symptoms.”
- The term applies to interventions started before or after biological evidence of the underlying disease, intended to postpone the onset, partially reduce the risk of or completely prevent symptomatic AD and that directly modify, indirectly modify or compensate for the brain changes associated with presymptomatic AD.
- Anticipates a definition of AD that includes different presymptomatic and symptomatic stages and a regulatory approval pathway for demonstrably effective presymptomatic AD treatments.

Now is the time to accelerate the evaluation of presymptomatic AD treatments

- With the skyrocketing number of people living to older ages, demonstrably effective presymptomatic AD treatments are urgently needed to avert an overwhelming crisis.
- A large number of healthy lifestyle and dietary interventions, dietary supplements and medications suggested, but not yet proven, to reduce the risk of symptomatic AD need to be tested in presymptomatic AD trials.

- An even larger number of investigational AD-modifying treatments are now being evaluated in symptomatic AD trials, some of which may soon have safety and tolerability data to trial in cognitively normal people at the highest imminent risk of symptomatic AD.
- Many of these treatments may be most effective if started prior to onset of symptoms, when extensive AD neuropathology is already evident.
- Brain imaging and cerebrospinal fluid biomarkers of presymptomatic AD progression and pathology could be used in cognitively normal groups at increased risk for AD to evaluate presymptomatic AD treatments in proof-of-concept clinical trials. At-risk groups might include *APOE* $\epsilon 4$ carriers, early-onset AD-causing mutation carriers or people with biomarker evidence of presymptomatic AD.

What is holding us back?

- It takes too many people, too much money and too many years to conduct adequately powered presymptomatic AD randomized clinical trials (RCTs) using clinical end points.
- Regulatory agencies will not approve a presymptomatic AD treatment based solely on biomarker end points until clinical trials show that a treatment's biomarker effects are reasonably likely to predict a clinical benefit.
- Public policies do not provide the funding or financial incentives needed to support more than a few time-consuming and expensive presymptomatic AD trials at a time.

Scientific proposals for AD treatments

- The following proposals have been suggested to accelerate the evaluation of presymptomatic AD treatments:
 - Conduct presymptomatic AD/surrogate marker development trials in cognitively normal early-onset AD-causing mutations carriers, close to their estimated median age at clinical onset, *APOE* $\epsilon 4$ homozygotes close to their estimated median age at onset and individuals with biomarker evidence of presymptomatic AD.
 - In the meantime, embedded multiple biomarkers in symptomatic AD trials to determine the extent to which a treatment's effects on different biomarkers, alone or in combination, are reasonably likely to predict a clinical benefit.
 - Establish the infrastructure needed to conduct multiple presymptomatic AD RCTs at the same time, including national AD prevention trial registries for future studies.
 - Implement this proposed Alzheimer's Prevention Initiative in the most careful and inclusive way.

Public policy recommendations

- The following public policy recommendations have been suggested to accelerate the evaluation of presymptomatic AD treatments:
 - Give pharmaceutical companies compelling financial incentive, such as extended marketing exclusivity, to conduct time-consuming and expensive trials of their most promising presymptomatic AD treatments.
 - Provide federal funding to evaluate presymptomatic AD treatments, for which a financial incentive may be lacking (e.g., available medications with

limited or no patent coverage, dietary supplements and health-promoting lifestyle interventions).

– Provide federal funding or tax credits for the inclusion of multiple complementary brain imaging and other biomarker measurements in RCTs of promising AD-slowing treatments, and a requirement for pharmaceutical companies to make the data publicly available after the trials are completed, to help in the development of surrogate end points for symptomatic and presymptomatic AD trials.

– Create the public–private partnerships needed to evaluate promising presymptomatic treatments and develop surrogate markers in the most rapid and rigorous way. This partnership would include leaders from academia, industry, federal and regulatory agencies, and other stakeholder groups.

Conclusion

- Let us establish an Alzheimer's Prevention Initiative with the sense of urgency, public policies, research infrastructure and presymptomatic AD treatment/surrogate marker development trials needed to find demonstrably effective presymptomatic AD treatments without losing a generation.

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102. A National Alzheimer’s Strategic Plan: the report of the Alzheimer’s Study Group www.alz.org/documents/national/report_ASG_alzplan.pdf ▪ Provides additional perspectives about the public policies and scientific strategies needed to accelerate the identification of demonstrably effective symptomatic and presymptomatic AD treatments.

Figure 1. The best established brain imaging biomarkers of Alzheimer's disease progression and pathology

(A) Fluorodeoxyglucose-PET studies find characteristic and progressive declines in regional cerebral metabolic rate for glucose in people with Alzheimer's disease (AD), as illustrated in this statistical brain map, comparing symptomatic AD patients and controls. (B) Structural MRI studies find brain shrinkage in people with AD, including (i) accelerated rates of atrophy in the Hi and ERC regions-of-interest; (ii) accelerated rates of whole brain atrophy using sequential MRIs, as shown in red in a symptomatic AD patient; (iii) a characteristic and progressive loss of gray matter, as shown in this statistical brain map comparing symptomatic AD patients and controls; and (iv) characteristic and progressive cortical thinning, as shown in this statistical brain map comparing symptomatic AD patients and controls. (C) PET studies of fibrillar amyloid- β ($A\beta$), as illustrated in this statistical comparison of Pittsburgh Compound-B PET measurements of fibrillar $A\beta$ in symptomatic AD patients and controls; fibrillar $A\beta$ PET studies using other radioligands are now under investigation. Several of the brain imaging measurements shown in this figure have been used to detect and track presymptomatic AD, and other brain imaging techniques are contributing to the early detection, tracking and scientific study of AD.

ERC: Entorhinal cortex; Hi: Hippocampus; Pa: Parietal; PF: Prefrontal; Te: Temporal.
Reproduced with permission from [26].

Figure 2. Correlations between *APOE* $\epsilon 4$ gene dose (the number of $\epsilon 4$ alleles in a person's *APOE* genotype, reflecting three levels of genetic risk for late-onset Alzheimer's disease [AD]) in 160 cognitively normal late-middle-aged persons and reduced CMRgl in posterior cingulate, precuneus, parieto-temporal and frontal preferentially affected by AD

This study and others have demonstrated the ability of FDG PET to detect and track characteristic CMRgl reductions in people at risk for late-onset and early-onset AD. Adapted with permission from [40].

Figure 3. Annual rates of whole brain atrophy in cognitively normal late-middle-aged people with two copies, one copy and no copies of the *APOE* ϵ 4 allele, reflecting three levels of genetic risk for late-onset Alzheimer's disease

Rates are reflected in terms of their means and SD. Other studies have demonstrated the ability to track rates of whole brain atrophy prior to symptomatic Alzheimer's disease in early-onset Alzheimer's disease-causing mutation carriers.

SD: Standard deviation.

Adapted with permission from [27].

Figure 4. Increases in Pittsburgh Compound-B PET measurements of fibrillar amyloid- β burden in cognitively normal adults (average age 63) with two copies, one copy or no copies of the *APOE* $\epsilon 4$ allele, reflecting three levels of genetic risk for late-onset Alzheimer's disease, and in symptomatic Alzheimer's disease patients

The statistical maps show no increases in $\epsilon 4$ noncarriers in comparison to the $\epsilon 4$ carriers, as well as increases in $\epsilon 4$ heterozygotes, $\epsilon 4$ homozygotes and symptomatic AD patients in comparison to the $\epsilon 4$ noncarriers. While longitudinal assessment is needed, the cross-sectional data shown here suggests that PET will be able to track progressive increases in fibrillar amyloid- β during this presymptomatic stage of AD, in contrast to the symptomatic stages of AD when fibrillar amyloid- β may have plateaued.

AD: Alzheimer's disease.

Adapted with permission from [31].

Figure 5. Pittsburgh Compound-B PET measurements of fibrillar amyloid- β burden in a presymptomatic carrier of an early-onset Alzheimer's disease-causing presenilin 1 mutation
As illustrated in this image, presymptomatic patients with several early-onset Alzheimer's disease-causing mutations appear to have unusually high levels of fibrillar amyloid- β in the striatum, as well as increased levels in cerebral cortex.
Reproduced with permission from [33].