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# Developing a national strategy to prevent dementia: Leon Thal Symposium 2009

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## Abstract

Among the major impediments to the design of clinical trials for the prevention of Alzheimer's disease (AD), the most critical is the lack of validated biomarkers, assessment tools, and algorithms that would facilitate identification of asymptomatic individuals with elevated risk who might be recruited as study volunteers. Thus, the Leon Thal Symposium 2009 (LTS'09), on October 27–28, 2009 in Las Vegas, Nevada, was convened to explore strategies to surmount the barriers in designing a multisite, comparative study to evaluate and validate various approaches for detecting and selecting asymptomatic people at risk for cognitive disorders/dementia. The deliberations of LTS'09 included presentations and reviews of different approaches (algorithms, biomarkers, or measures) for identifying asymptomatic individuals at elevated risk for AD who would be candidates for longitudinal or prevention studies. The key nested recommendations of LTS'09 included: (1) establishment of a National Database for Longitudinal Studies as a shared research core resource; (2) launch of a large collaborative study that will compare multiple screening approaches and biomarkers to determine the best method for identifying asymptomatic people at risk for AD; (3) initiation of a Global Database that extends the concept of the National Database for Longitudinal Studies for longitudinal studies beyond the United States; and (4) development of an educational campaign that will address public misconceptions about AD and promote healthy brain aging.

### Keywords

Alzheimer's disease; Dementia; Mild cognitive impairment; Prevention; Biomarkers; Diagnosis; Screening; Clinical trials; MCI; Asymptomatic; Risk factors; Registry; Longitudinal studies; Database; PAD2020; Leon Thal Symposium; Treatment; Drug development; Health policy



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## 1. Introduction

The series of Leon Thal Symposia (LTS), which began in 2007, have been organized to honor Leon Thal's contributions to the field of therapy development for Alzheimer's disease (AD). Theses annual *think-tank* style meetings are organized to provide key leaders in Alzheimer's research a forum for strategic thinking and formulating national policies to move forward the campaign on prevention of AD.

In 2008, the Leon Thal Symposium (LTS'08) formulated a plan [1], which was incorporated in large part into the report of the *Alzheimer's Study Group (ASG)* presented to the 111th Congress on March 24, 2009. The ASG report recommended *prevention* as a key priority for a proposed National Alzheimer's Strategic Plan. Subsequently, the recommendations of LTS'08 report–"Road Map for Prevention" and the ASG report–were incorporated into *The Alzheimer's Breakthrough Act of 2009*–(S 1492 and HR 3286) [2]. This authorizing legislation proposes to double the ceiling for funds allocated for Alzheimer's research by the National Institutes of Health for fiscal year 2010. The bills also call for a National Summit on Alzheimer's, which will bring together scientists, policy makers, and public health professionals to move the enterprise forward.

In 2009, the *Campaign to Prevent Alzheimer's Disease by 2020*[1] (also referred to as PAD2020) was incorporated to maintain the momentum of the ASG and put into action the recommendations for a *National Strategic Goal* aimed at reducing the prevalence of AD and other related brain-behavior disorders.

## 2. Objectives of LTS'09

Presently, among the array of impediments to prevention[2] studies, the most critical factors are the lack of: (a) validated algorithms, biomarkers, and assessment tools to facilitate the identification of asymptomatic people with elevated risk for AD; (b) research resources or infrastructure for large scale longitudinal studies; and (c) a national/international database on asymptomatic volunteers with elevated risk who might be recruited as potential research volunteers.

Thus, the LTS'09, on October 27–28, 2009 in Las Vegas, Nevada, was convened to plan for a national initiative and the establishment of the infrastructure needed to facilitate the following:

- Discovery and validation of early risk factors and biomarkers

[1]Prevent Alzheimer's Disease 2020 Inc. (PAD2020) is a Maryland based 501(c)(3) not-for-profit corporation. The PAD2020 campaign is a call to arms; organized to put into action the recommendations of the Alzheimer's Study Group (ASG). The primary focus of the campaign is to develop a comprehensive 10-year implementation plan, including budget estimates, for a National Strategic Goal aimed at reducing the prevalence of Alzheimer's disease and other related brain-behavior disorders. PAD 2020 articulates a simple vision that is compelling enough to rally broad national support for a 10-year strategic plan for sustained and systematic investment of funds designed to: a) expand research on the neurobiology of neurodegeneration; and b) build national capacity for prevention of memory, movement and mood disorders.

[2]The Campaign to Prevent Alzheimer's Disease 2020 (http://www.pad2020.org) and the Leon Thal Symposia (LTS) define the concept of *prevention* in the broadest possible terms. The ultimate aim of PAD2020 and the LTS is to promote the development of broad spectrum interventions, including, but not limited to, primary, secondary and tertiary prevention strategies that are designed to maintain independent functioning and/or delay the onset of disabling symptoms for as long as possible.

- Development of algorithms for identifying asymptomatic people at risk
- Design and management of multisite, comparative studies to evaluate and validate various approaches for detecting asymptomatic people at risk for cognitive disorders or dementia
- Creation of a national database (registry) of asymptomatic people at risk for memory disorders

The meeting focused centrally on establishing a *National Database for Longitudinal Studies (NDLS)* as a shared core research resource. The NDLS would serve as a dataset exchange-network for various singular and inter-related applications. For example, this database is essential for characterizing the natural history of various forms of memory disorders throughout the lifespan of individuals with elevated risks for developing AD. Also, large-scale longitudinal studies of people at risk for dementing disease are needed to validate assessment tools. In turn, such tools are urgently needed for anticipated therapeutic and eventual preventive trials. The dearth of these tools remains a rate-limiting issue for validating the concept of AD prevention.

The creation of a national database or a registry of asymptomatic volunteers with elevated risk for memory disorders or dementia is a complex and critical first step. The effort will involve recruiting large numbers of healthy people who are willing to undergo an initial set of assessments so that a baseline dataset can be established. From this cohort, subgroups may be selected for additional studies to evaluate different methods of identifying the earliest predictors of disease. Validated tools will permit selection of appropriate individuals, either those with “elevated risk” or “at-risk,” for randomized clinical trials. Furthermore, these new technologies will serve to demonstrate whether a therapeutic agent is having a positive effect, so that future prevention and therapeutic trials can be accomplished in a reasonable time frame.

## 3. Discussion points

### 3.1. Constructing the cohort

A number of longitudinal cohorts have been established to study aging and dementia. For example, the Mayo Clinic Study of Aging recruited a population-based cohort to investigate prevalence, incidence, and risk factors for mild cognitive impairment (MCI) and dementia. Subjects were randomly selected from a population of nondemented individuals who were aged 70–89 years at baseline and living in a restricted geographical area (Olmsted County, Minnesota) [3]. A total of 2719 participants were recruited and are seen annually for follow-up. Assessments include clinical evaluation, risk factor assessment (e.g., family history and medical history), neurological evaluation, and neuropsychological assessment, with a subset studied more extensively through fluorodeoxyglucose–positron emission tomography (PET) and amyloid imaging studies, collection of cerebrospinal fluid for biomarker analysis, and collection of DNA for genetic studies. Sampling in a population-based manner for this study was relatively easy, as the Mayo Clinic and the Olmsted Medical Center, which cooperate fully with Mayo, are the only care providers in Olmsted County, and they have the luxury of geographic confinement. Thus, the study reports a good follow-up rate as well as a good

autopsy rate. However, translating this model to a broader community could be challenging, and will require a distillation of the core features that need to be assessed as well as the best instruments. Nonetheless, it provides a template for longitudinal studies on a national scale.

Other longitudinal studies have used samples of convenience rather than population-based samples, and each of these models has advantages and disadvantages. Although the national registry will almost certainly enroll a heterogeneous group of subjects, individual studies may select subgroups from that registry depending on the goals of the study, and early studies will likely be more homogeneous. For example, trials of preventive therapies would be greatly expedited if the study population could be enriched for those at high risk of developing AD within a relatively short time period, although such individuals may have had a longer asymptomatic period of AD and may therefore be less responsive to prevention therapy. A complementary approach would be to enroll asymptomatic individuals and use a quantitative AD biomarker as a measure of prevention therapy efficacy. Whatever enrollment strategy is selected, the cohort should include individuals with a wide rage of education levels and multiple racial backgrounds, since there appears to be an increased prevalence of dementia in nonwhites, and education level has been identified as a major risk for dementia.

A *North American database for longitudinal study* (an expanded version of a US national database) could share design elements, and perhaps a common set of variables, with a wide spectrum of other ongoing epidemiological and/or longitudinal databases or studies. For example, at least one massive effort in North America–the Canadian Longitudinal Study in Aging [4] could provide the foundation for building a network of data-sharing linkages. The Canadian Longitudinal Study in Aging has been recently launched with the goal of enrolling 50,000 Canadian men and women aged more than 40 years, and to follow-up these subjects for at least 20 years.

### 3.2. Predicting who will get disease

One way of selecting those individuals who are at high risk of developing disease is to develop and apply risk indices, which combine different measures to create a summary score. The accuracy of these indices is based on the area under a receiver operating characteristic curve, also known as the *c* statistic. The *c* statistic may range from 0 to 1, with 1 representing a perfect prediction and 0.5 representing no better than guessing. A c statistic of 0.75 suggests that the index provides a pretty good risk indicator. Perhaps the best known example of a risk index used to identify individuals at risk for a particular disease is the Framingham index, which identifies cardiovascular disease risk [5]. The Framingham index has a *c* statistic of 0.79. In contrast, a commonly used Breast Cancer Risk Assessment Tool [6] has a *c* statistic of only 0.58, which is not much better than guessing.

A late life dementia risk index has been developed and used in people aged ≥65 years with no signs of dementia [7]. This index incorporates age, scores on the Modified Mini-Mental State Exam and Digit Symbol Substitution Test; low body mass index; magnetic resonance imaging (MRI) findings of white matter disease or enlarged ventricles; carotid artery thickening on ultrasound; history of coronary artery bypass surgery; presence of at least one apolipoprotein E (*APOE*) ε4 allele; slow physical performance; and lack of alcohol

consumption. With a *c* statistic of 0.81, this index thus can accurately identify individuals with high dementia risk. However, in certain situations, such as in recruiting subjects for clinical trials or identifying high-risk individuals in clinical settings, it will be important to reduce subject as well as clinician or investigator burden. For such situations, the index has been modified to create a Brief Dementia Risk Index that incorporates only demographics, medical conditions, selected items from the Modified Mini-Mental State Exam and Center for Epidemiologic Studies-Depression Scale that assess cognitive and psychosocial functions, and behavioral measures. The Brief Dementia Risk Index has a *c* statistic of 0.77, which although significantly lower than that of the full index, still represents high accuracy. The Brief Dementia Risk Index is described in more detail in the accompanying article on pages 139–142 [8].

A Mid-Life Dementia Risk Score also has been developed for use in individuals aged 40–64 years [9]. This tool uses a combination of age, gender, education, physical inactivity, and history of obesity, hypertension, and hypercholesterolemia to predict risk of dementia 20 years later. With a *c* statistic of 0.77, this index also has fairly high accuracy. Inclusion of *APOE* $\varepsilon$4 genotype increased the prognostic accuracy of the index slightly to 0.78.

Thus, dementia risk indices represent a practical approach for identifying high-risk individuals. However, different indices may be needed for different uses, that is, in clinical vs. research settings or in studies of mid-life vs. late-life interventions. Additional studies are needed to validate these indices in various study populations. Moreover, risk indices such as these will be improved over time with the addition or substitution of new and minimally invasive risk markers as they become validated and deemed to be fit for use (e.g., novel gene expression markers of early disease).

A different approach was used to identify a high-risk group of asymptomatic middle-aged individuals for the Wisconsin Registry for Alzheimer's Prevention, which began in 2002 [10]. For this study, adult children of people with AD were recruited through a 30-second television spot. Within 24 hours after airing this spot, the Institute's phone lines were overwhelmed with 600 calls. They now have 950 well-characterized volunteers from every county in Wisconsin, who come to Madison for a comprehensive set of neuropsychological studies. A subset also participates in neuroimaging studies (discussed later in the text). After four years, they have had only a 10% attrition rate, and the success of this recruitment and retention effort demonstrates that family history is a very motivating factor for longitudinal and prevention studies. Moreover, this population was found to have a high prevalence (approximately 45%) of *APOE* $\varepsilon$4. Interestingly, however, the researchers found baseline cognitive and neuroimaging findings suggestive of AD that are independent of *APOE* $\varepsilon$4 genotype, suggesting that other families of genes and polymorphisms may be at least as important for identifying those at early risk for AD.

### 3.3. Genetic variants, genomics, and disease prediction

As an example, one possible polymorphic gene variant is found in the translocase of the outer mitochondrial membrane 40 (TOMM40) gene, which sits adjacent to the APOE (the gene *APOE* encodes the lipid transporter apolipoprotein E [apoE] and has three common alleles [$\varepsilon$2, $\varepsilon$3, and $\varepsilon$4] that afford six diploid genotypes) gene on chromosome 19 and

encodes the TOMM40 enzyme. This enzyme may play a role in transport of proteins across the mitochondrial membrane. The *APOE* ε4 gene variant, identified in 1993 by Allen Roses and colleagues, has been shown to confer a high risk of developing late-onset AD, and to this day it remains the strongest genetic predictor of risk, although the correlation is too weak to use as a diagnostic test because many individuals with *APOE* ε4 never get AD and others with the more common variant, *APOE* ε3, do. More recent work suggests that TOMM40 gene variants have an even stronger relationship with age of onset than *APOE* variants. Using phylogenetic mapping to map variants in the TOMM40 gene to age of onset, the TOMM40 gene was shown to exist in either a short, long, or very long form based on polymorphic poly-T repeat variants. Further, long forms were shown to correlate with earlier age of onset. Because *APOE* and TOMM40 are closely spaced within chromosome 19, they mostly are inherited together. *APOE* ε4 is almost always associated with long forms of TOMM40, whereas *APOE* ε3 may be associated with a very long or a short form. In studies of two independent clinical cohorts of late-onset AD patients with ε3/3, ε3/4, and ε4/4 genotypes, patients with the *APOE* ε3/4 genotype and long poly-T repeats developed AD at an average of 7 years earlier than *APOE* ε3/4 carriers with short repeats. *APOE* ε3/3 patients can have either short/short, short/long, or long/long repeats and, indeed, the age of onset for *APOE* ε3/3 patients covers a broad range. Early data (unpublished) suggest that *APOE* ε3/3 patients with two very long repeats could have even earlier age of onset than *APOE* ε4/4 patients (presently the numbers are far too small to use any other word than “could”; data on 4000–5000 patients is being analyzed to validate this assertion).

Validating the use of *APOE*/TOMM40 genotyping as a means of identifying high-risk individuals could take 5–7 years. It is also possible to validate the predictions using the TOMM40 data by examining prospectively collected cohorts that have been followed for 5–18 years for which DNA had been obtained. Several investigative groups are collaborating with Roses and colleagues to look at a total of about 10,000 individuals. These retrospective studies of prospectively collected data have been initiated, with first results available in 2010. However, of importance to the prevention theme, it is also possible to incorporate a diagnostic validation study within a clinical trial to test the ability of a particular drug to prevent or delay onset of the disease. Moreover, several scientists made the point that, until validation of the TOMM40 data has been accomplished, enriching prevention trials is now feasible using the combination of age and genotype, including *APOE* ε4 as well as a number of dominantly inherited forms of presymptomatic AD.

Other genetic variants may also be useful in predicting who will get AD or other forms of dementia. The technology for gene sequencing has undergone an explosion in recent years, resulting in genome-wide association studies that have identified genetic variations associated with more than 40 common diseases. An Alzheimer's Disease Genetics Consortium has been established with funding from the NIA to conduct a genome-wide association studies study with data and DNA samples gathered from large numbers of affected individuals and controls through 29 Alzheimer's Disease Centers. In addition to sequencing the DNA from these individuals, the Consortium is compiling data collected using the uniform data set at the Alzheimer's Disease Centers as well as neuropathological and biomarker data on these subjects. Over the next few months, 5000–6000 cases and a

similar number of controls could be in joint data analysis. In addition, the Consortium is setting up the infrastructure to collaborate with other investigators who have assembled other cohorts, possibly allowing them to ramp up to as many as 50,000 cases and 50,000 control subjects.

The presence of genetic variants may predict the development of AD; however, rather than looking at static measures, such as genotype, another possibility is that variations in gene expression, which provide a dynamic measure of the current state of the individual, may help differentiate normal from asymptomatic individuals. This genomics approach is based on the assumption that AD is a systemic disease, and may manifest itself by altering gene expression in a number of systems outside of the central nervous system and in particular, peripheral blood cells. ExonHit Therapeutics, Inc. has built a microarray platform with over six million probes that monitor the expression of different splice variants throughout the entire genome. Comparing the expression profiles of blood samples from AD patients against controls, they have identified 170 probes (short, expressed RNA sequences) that appear to differentiate AD patients from normal subjects with 71% accuracy. The signature has been shown to be dependent on the disease state and independent of treatment. In addition, this collection of probes may also be applicable in detecting presymptomatic individuals, where the profile changes can occur before any appearance of cognitive decline, similar to the early changes seen for cerebrospinal fluid (CSF) biomarkers. This technology could be useful in pharmacogenomic applications to identify patients that are more likely to respond to a particular treatment. Expression profiles can change depending on the health of the individual, and it is highly probable that the 170 probe collection can monitor disease progression and regression, and identify effective treatments that result in patients reverting to a healthier profile. Further studies are needed with larger cohorts and comparisons to other measures (imaging, CSF, etc) to validate this approach.

### 3.4. Other measures for identifying disease risk

A number of other measures may also be useful in detecting change in asymptomatic AD, that is, in people who are cognitively and functionally normal, though they have AD changes in brain and will eventually develop symptoms of the disease. These include imaging measures (both structural and functional), CSF biomarkers, and cognitive assessments.

Structural imaging has shown that in AD brains, atrophy resulting from neurodegeneration begins long before symptoms appear; however, it is possible that functional changes that reflect amyloid accumulation, metabolic changes, or synaptic dysfunction may appear even earlier. Indeed, functional assessments, including arterial spin-labeled perfusion, functional MRI, diffusion tensor imaging, and fluorodeoxyglucose and Pittsburgh Compound-B PET have all shown promise in identifying asymptomatic AD. For example, in an functional MRI study of cognitively normal middle-aged adults given an episodic encoding task, blood oxygen level dependent signal changes were more pronounced in individuals (mean age, 53 years) with a family history of AD or in those who carried the *APOE* $\varepsilon$4 allele [11], supporting the idea that functional brain changes are among the earliest signs of AD. The variance was more strongly related to family history than to presence of the *APOE* $\varepsilon$4 allele,

again suggesting that some genetic variant other than *APOE* ε4 increases the risk of developing AD. Similar family history effects were observed with a molecular structural imaging approach [12] in subjects (mean age, 57) recruited from the same cohort. Mosconi et al have found PET glucose metabolism differences in subjects (mean age, 63) with maternal family history [13,14]. In all three studies, the effects were present after controlling for *APOE* genotype. Roses has also committed to genotype the TOMM40 length polymorphisms for this family history series to be analyzed as well, since the polyT length variation accurately classify two distinct phylogenetic groups of TOMM40 attached to *APOE* ε3 genes, independent of *APOE* ε4 effects.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) was organized as a longitudinal study to evaluate and standardized a variety of assessment measures, including neuroimaging measures and CSF derived biomarkers from well characterized people with AD in early stages of the disease. The first report on studies of baseline CSF samples from ADNI subjects was recently published [15]. This report showed that a baseline CSF profile for t-tau/$A\beta_{1\text{-}42}$ could be used to detect mild AD with very high sensitivity and specificity. Now the field is getting ready, thus the LTS'09 meeting, to build the infrastructure and assessment tools to conduct longitudinal studies similar to ADNI, but with the inclusion of large numbers of asymptomatic people at elevated risk several years or even decades before the onset of symptoms.

Meanwhile, the search is on for novel biomarkers that might provide better sensitivity and specificity, particularly in the earliest stages of the disease. Proteomics approaches have been tried by several groups and can distinguish normal from AD with reasonable confidence, but so far have not yielded robust and reproducible findings. Other approaches that may be revealing include assessment of metabolites (metabolomics), the use of protein microarrays to study post-translational modifications such as ubiquitination, or the use of multiplex analyte panels to measure changes in peptides and proteins in the CSF. These analytes could be, for example, inflammatory markers, trophic factors, or brain-secreted peptides that reflect early steps in AD pathogenesis. Individually, none of these approaches may provide the sensitivity needed to assess risk; however, it may be possible to improve the accuracy of early identification by combining several of these approaches, for example, combining genotyping with measurements of analytes in the serum and with the CSF biomarkers t-tau and $A\beta_{1\text{-}42}$.

Improved behavioral tools could be helpful in assessing very early cognition changes, as “behavioral-biomarkers” or predictors of ‘risk’ for cognitive impairment. Presently, here are numerous measures with good sensitivity (eg, paired associate learning tests) to assess cognition in asymptomatic people. However, for such tests to be useful in a large study, they will have to be brief, easy to understand, and easy to administer in a standardized manner, with everyday equipment by nonexperts; free of practice effects; insensitive to fatigue and motivational changes; have good test-retest reliability; and have desirable statistical properties, including a normal distribution, no floor or ceiling effects, and a small coefficient of variation. Beyond these psychometric characteristics, data delivery, transmission, management, and storage must be rigorously controlled. Importantly, it will be essential to report data back to users quickly so that discrepancies can be corrected. Because participants

would be assessed repeatedly over many years, the measures must be appropriate for individuals across the lifespan and be able to detect subtle changes. Home-based assessments, if available, could increase compliance with the study and reduce participant burden.

Web-based assessment tools could also prove useful in a large longitudinal study, particularly if they can be administered either in person or by telephone, automatically scored and interpreted, and longitudinally tracked. One such tool is the MCI Screen, which is a modification of the Consortium to Establish A Registry for Alzheimer's Disease (CERAD) Wordlist. The MCI Screen uses 16 statistically and linguistically equivalent word list and measures patterns of recall, and has been extensively tested in 250,000 subjects. To determine whether the tool can identify asymptomatic individuals, a subsample of individuals aged more than 65 were tested. The tool correctly classified 87% of the impaired group and 94% of the normal subjects. Further refinements of the tool are needed to ensure cultural appropriateness. In addition, cognitive processing models combined with Bayesian methods may enhance the ability of the tool to make better predictions about individuals.

### 3.5. Measurement challenges

One of the major challenges to moving forward with preventive therapies is that while there have been significant improvements in tests designed to detect change in people with MCI and AD, currently available measures are still not sensitive enough to measure change in asymptomatic individuals. Now that attention is shifting to the prodromal period, new techniques are needed to assess changes. Moreover, we currently lack sufficient information about pathophysiology during this transitional period. In fact, no comprehensive model of the disease that takes into account all the various aspects of the disease – genetics, pathophysiology, cognition, behavior, etc. – exists, either in the prodromal or manifest stages. However, there is evidence to suggest that pathogenesis during the asymptomatic phase may be significantly different from later on in the disease. In addition, during the asymptomatic phase, although there is presumably both biochemical and anatomical pathology emerging, there is also a dynamic mechanism of compensation within the brain. This means that for some forms of testing, for example, neuropsychological testing, successful compensation may mask any dysfunction. By incorporating cognitive processing models into the strategy by which an individual performs a neuropsychological test, it may be possible to detect compensation for dysfunction. Additionally, biomarkers of synaptic plasticity or dendritic pruning, which might reflect some of these compensatory mechanisms, are needed. In addition to the confounding effect of compensation, lifestyle issues have emerged as important determinants of disease progression. Thus, we may be missing important information by not looking at the effect of diet, exercise, sleep, etc. on biomarkers and neuroimaging. The same could be said about co-morbidities and their effects on biomarkers and other measures.

Yet while there is still much to learn about the prodromal phase, there is a convergence of biological and imaging markers, suggesting that it would be reasonable to begin validating new cognitive paradigms against a convergence of these biological measures. This might require establishing a core set of measures, including behavioral, neuropsychological,

imaging, and biomarkers, which could be used across the board in studies so that data could be compared. Moreover, we are entering a time in which large complementary data sets are being acquired in many individuals. These data points include brain images with thousands and thousands of voxels of information, transcriptomic data, demographic data, etc. One of the challenges is to learn how to capitalize on this wealth of data with multimodal analysis techniques. Multiple measures could, for example, be put into hierarchical algorithms that allow one to measure multiple levels of the state of an individual's nervous system–from genomic to behavioral. Such hierarchical measures of brain state and function could give a more comprehensive assessment of an individual to help identify people at risk. However, some measures, for example, functional imaging, may not be useful in this regard because the techniques are not amenable to large population studies.

### 3.6. Selecting the study population

An additional complication in terms of validating measures is that different measures may be appropriate for different populations, and the question of heterogeneity of the population thus becomes even more important. Homogeneous samples may be necessary to expedite trials and limit their duration, and different populations will allow specific questions to be addressed. For example, dementia in younger people may be different from a pathophysiological perspective than that in older people, so including both groups in a single study could obscure some important information. However, unless one looks at a heterogeneous sample, one will not know which sources of heterogeneity are relevant to the disease. Moreover, there has been a striking lack of diversity in many of the studies conducted so far. Sampling from the Veterans' Administration could help address this lack of diversity (especially if spouses are included), and might also have other data collection advantages because of the availability of electronic medical records. PAD2020's efforts to continue the establishment of a European Union-North American globally-pooled, shared-data resource should provide additional access to other populations [16]. One possible way of selecting individuals at high risk for certain studies would be to start with a heterogeneous sample and then enrich it in a stepwise manner, first on the basis of family history, then on genetic screening, then adding risk assessment indices.

## 4. Moving forward–are we ready?

Until recently, prevention trials have been conducted for practical reason at later stages of the disease (eg, MCI, mild or moderate), where it is simpler to identify decline and assess outcomes with the available measures. These trials, largely based on experiences with symptomatic treatment have been disappointing. Now, there is growing recognition in the field of AD that by the time symptoms are recognizable, the disease has progressed much too far to be reversed or even to change the outcome appreciably.

Although there is substantial consensus on the need to move toward earlier and earlier interventions, the effort to re-focus research on detection/diagnosis and treatment of the disease in the presymptomatic stages faces a number of impediments, which include: (a) conceptual difficulty in defining and measuring the disease in the very early asymptomatic, presymptomatic, or prodromal stages preceding MCI; (b) a lack of agreement on whether the disease represents a continuum of neurodegenerative process ranging from the

asymptomatic phase through the stages MCI, mild, moderate, and severe; (c) a lack of well defined or validated markers or indices for these early asymptomatic stages of the “disease” (d) a lack of criteria and tools to identify asymptomatic individuals at risk for the disease; and (e) a lack of agreement on a well defined measurable “outcomes” to monitor the progression of the disease.

The discussions at the LTS'09 meeting were fueled by the premise that we need to move the AD research enterprise to the point where interventions are applied earlier. However, the question of how early in the disease process we can intervene will depend on the capabilities and algorithms we develop to synthesize information from several domains that might include: genetics, genomics, cognitive assessment, imaging, CSF biomarkers, and other information from asymptomatic people at elevated risk.

The question of whether we are ready to move forward pits those who want to begin another series of primary prevention trials with existing knowledge against those who think more preliminary work is needed. On the one hand, without a more fundamental understanding of the disease, we may be doomed to repeat past mistakes. On the other hand, perhaps the greatest roadblock to finding asymptomatic treatments may not be in understanding the disorder, but in determining how to evaluate treatments that are already available in the most rapid and rigorous way, for example, by focusing on scientific methods to evaluate multiple treatments in shorter studies as well as modifying the regulatory approval pathway to incentivize multiple stakeholders to invest in these studies.

Lessons from previous studies dictate that primary prevention trials to date have been long (many years), costly (average, >$30 million per study), and have involved thousands of subjects. Ideally, studies of the future will be shorter and focus on a specific target. However, concerns about their generalizability will linger. The ultimate challenge is to identify those who will definitely develop AD in their lifetime and develop intervention strategies to forestall or prevent the disease. The second generation primary prevention trials will use a combination of improved enrichment strategies and selection of biomarkers.

Tradeoffs will undoubtedly be necessary in assessing the tolerability of potential risks. It is important to consider the risks of intervention (eg, drug side effects) in the context of potential benefits that may include improved quality of life, delaying the onset of disabling symptoms, or postponing institutionalization. Regardless of how “high-risk” individuals are identified, some percentage of them will never develop symptomatic disease. Therefore, intervention in these individuals may expose them to unnecessary risk. It may be helpful to lay out all the alternative approaches in a grid, considering for each one the biological plausibility, evidence for safety as well as efficacy, operational risks, costs, regulatory issues, and potential market considerations. Within a framework such as this, it may become clearer what trade-offs will be necessary, what strategies may be most fruitful, and how the field can move forward with both deliberation and urgency, since both are needed.

## 5. Actionable recommendations

### 5.1. Establish a national database for longitudinal studies–a “registry”

Despite the range of opinions as to the best path forward, ranging from focusing more on the fundamental biology of the disease to the view that it is now time to move forward with prevention trials, a consensus emerged on the value of establishing a NDLS. A registry would not only provide a mechanism for expediting recruitment, which has been the rate limiting step in conducting trials [17], in addition it could also raise awareness among the population about the impending crisis.

The goal of the overall initiative would be to prevent cognitive decline in aging. Thus, it would make sense to target those who have a family history of AD or cognitive decline as the first recruits into the registry. Then it would be necessary to screen people effectively. Initially, screening would be limited; however, as investigators develop specific studies that could take advantage of the subpopulations in the cohort, they might access the registry to find subjects willing to undergo additional screening or provide DNA or blood samples for genotyping. Building the registry should lead to a longitudinal cohort study, since frequent serial assessments in a large population could allow investigators to plot the trajectory of change over several years, thus accumulating the data needed to reduce the total duration of clinical trials.

The prototype for this registry has already been developed for the Nevada Vital Aging initiative [18], and then further refined at a meeting in Barcelona to plan a European Union-North American collaboration [16]. In both of these cases, the planned registries were not driven by any particular hypothesis, but only by the general criteria of enrolling baby boomers. Then, various risk factors were added. A cohort such as this, with a minimal dataset, could then serve as a pool from which one could pull together subjects with particular characteristics for a specific study. By linking use of the registry to a funding mechanism, investigators could be encouraged to develop studies that would make best use of the cohort and provide additional information to enrich the database. There is already evidence from the Healthy Brain Aging and Memory Study that supports the feasibility of this approach, and demonstrates that a huge amount of data can be collected in a very centralized way using either low-or high-tech survey technology [19].

To gain maximal participation in such a registry and minimize sample bias, it will be important to do things that attract the target population and keep them enrolled. Such things could include providing specific information about an individual' AD risk factors and what might reduce risk, as well as more general information about what can currently be done to delay AD progression with currently available treatments.

### 5.2. Compare screens to determine which are best

Consensus was also reached on the probability that multiple screening approaches will be required to identify individuals who are at high risk for developing AD. A workgroup will be formed by *PAD 2020* to further evaluate the screening approaches discussed previously and to formulate a plan to evaluate which combination of screens would be needed at baseline, and then which assessments might be added for smaller subgroups of subjects.

PAD 2020 is the new sponsoring organization that will convene this, as well as several other workgroup(s) to formulate actionable plans for public policy initiatives. A National Registry and Clinical “Test Bed,” might enroll 10,000 households across the United States to participate in noninvasive home monitoring techniques; provide saliva or blood samples for genomic analysis; participate in home assessments of diet, lifestyle, and family, medical, and social histories; and collect water, soil, and air samples in the home. Then these households could be divided (either randomly or by some predetermined criteria) into subgroups to undergo: (a) wet biomarker studies and structural imaging, (b) cognitive testing, (c) functional imaging, and (d) other tests.

### 5.3. Address public misunderstandings about AD

Despite the huge public health implications of the growing AD problem, there is a high level of public misunderstanding about AD and healthy brain aging. For example, “brain games” have been successfully marketed as effective in slowing dementia despite a lack of scientific evidence, whereas the effectiveness of exercise, which has been documented (to a limited extent), is less widely accepted [20]. Because a person's level of understanding correlates with his or her willingness to participate in clinical trials and since recruitment for trials is so important, the need to address the public understanding of the issues is critical.

### 5.4. Go global–extending the registry beyond the United States

Although the current effort is to establish a registry in the United States, the problem of AD is a global one, and will require worldwide cooperative efforts if it is to be addressed effectively. As mentioned earlier, a European Union-North American collaboration was initiated in Barcelona last year. ADNI is also going global; for example, the Australian Imaging, Biomarkers and Lifestyle study of aging in many ways mirrors ADNI, and has also spun off some smaller initiatives to look at a asymptomatic cohort for evidence to explain a decline in cognitive function in the absence of known explanatory factors such as drug side effects. A global initiative is also underway in Canada, which has so far developed a partnership with France and is now in discussions with other European countries and the United States. Studies in Canada and some other countries will benefit from the presence of national health systems that ensure care and treatment for all citizens. In France, President Sarkozy last year unveiled a 5-year plan to invest $2.4 billion (1.6 billion euros) in a foundation for AD research.

## 6. Conclusion

AD is a prototype for other chronic brain disorders, and an excellent illustrative model for the health economics of a broad range of chronic disorders that require long-term, labor-intensive, and expensive care.

AD is destined to become a significant cost component of the pending health care crisis facing the aging cohort of 78 million baby boomers in whom the prevalence of various forms of brain disorders that impair memory, movement, or mood functions will increase exponentially.

The Congressional Budget Office estimates that total national spending on health care has more than doubled as a share of gross domestic product (GDP) over the past 30 years. The Congressional Budget Office further expects that this share will double again to 30% of GDP by 2035, 40% of GDP by 2060, and almost 50% by 2082 [2]. Federal spending on Medicare and Medicaid, which accounts for 4% of GDP today, is projected to rise to 9% by 2035 and 19% by 2082 under current law.

Now more than ever, the combined effects of demographic changes due to the ever-increasing lifespan and the looming financial catastrophe facing the health care system underscore the urgency of a *National Strategic Goal* to mitigate or forestall this disease. The campaign to *PAD 2020*, which was conceived based on the recommendations of LTS'07 and LTS'08, is being organized to formulate a national action plan to move the field toward developing the knowledge and capabilities for early detection and treatment of the disease in presymptomatic stages.

The launch of the PAD 2020 campaign, which represents a platform for strategic planning process, is envisioned as a benchmark for addressing a spectrum of other brain-behavior disorders that hamper independent functioning. The campaign considers “Alzheimer's” merely a prototype for a larger health care problem associated with a range of chronic brain disorders that have similar health economic profile to AD.

The proceeding and recommendations of the current symposium (LTS'09) represent another step forward on the path to prevention, but will require the sustained effort of all involved to ensure continued progress. The recommendation of LTS'09 think tank will be incorporated, along with other think-tank or Work Groups being organized by PAD 2020 during the fiscal year 2010, into a single strategic plan for legislative initiatives. (See PAD 2020 website for further details).

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## References

1. Khachaturian ZS, Snyder PJ, Doody R, Aisen P, Comer M, Dwyer J, et al. A roadmap for the prevention of dementia II: Leon Thal Symposium 2008. Alzheimers Dement. 2009; 5:85–92. [PubMed: 19328434]
2. The Alzheimer's Breakthrough Act of 2009, S 1492 and HR 3286, 111th Cong, 1st Sess (2009).
3. Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. Neuroepidemiology. 2008; 30:58–69. [PubMed: 18259084]

4. Raina PS, Wolfson C, Kirkland SA, Griffith LE, Oremus M, Patterson C, et al. The Canadian Longitudinal Study on Aging (CLSA). Can J Aging. 2009; 28:221–9. [PubMed: 19860977]
5. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998; 97:1837–47. [PubMed: 9603539]
6. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989; 81:1879–86. [PubMed: 2593165]
7. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: the late-life dementia risk index. Neurology. 2009; 73:173–9. [PubMed: 19439724]
8. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Commentary on "Developing a national strategy to prevent dementia: Leon Thal Symposium 2009." Dementia risk indices: A framework for identifying individuals with a high dementia risk. Alzheimers Dement. 2010; 6:139–42.
9. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol. 2006; 5:735–41. [PubMed: 16914401]
10. Sager MA, Hermann B, La Rue A. Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin registry for Alzheimer's prevention. J Geriatr Psychiatry Neurol. 2005; 18:245–9. [PubMed: 16306248]
11. Johnson SC, Schmitz TW, Trivedi MA, Ries ML, Torgerson BM, Carlsson CM, Asthana S, Hermann BP, Sager MA. The influence of Alzheimer disease family history and apolipoprotein E epsilon4 on mesial temporal lobe activation. J Neurosci. 2006; 26:6069–76. [PubMed: 16738250]
12. Bendlin BB, Ries ML, Canu E, Sodhi A. White matter is altered with parental family history of Alzheimer's disease. Alzheimers Dement. 2010 in press.
13. Mosconi L, Brys M, Switalski R, Mistur R, Glodzik L, Pirraglia E, Tsui W, De Santi S, de Leon MJ. Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism. Proc Natl Acad Sci USA. 2007; 104:19067–72. [PubMed: 18003925]
14. Mosconi L, Mistur R, Switalski R, Brys M, Glodzik L, Rich K, et al. Declining brain glucose metabolism in normal individuals with a maternal history of Alzheimer disease. Neurology. 2009; 72:513–20. [PubMed: 19005175]
15. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol. 2009; 65:403–13. [PubMed: 19296504]
16. Khachaturian ZS, Camí J, Andrieu S, Avila J, Boada Rovira M, Breteler M, et al. Creating a transatlantic research enterprise for preventing Alzheimer's disease. Alzheimers Dement. 2009; 5:361–6. [PubMed: 19560106]
17. Snyder PJ, Papp KV, Bartkowiak J, Jackson CE, Doody RS. Recruitment of participants for Alzheimer's disease clinical trials: the role of trust in caregivers, clinical researchers, regulatory authorities and industry sponsors. Alzheimers Dement. 2009; 5:122–4. [PubMed: 19328439]
18. Thal L, Kuller L, Bowman K, Breitner J, Evans D, Farrer L, et al. The Nevada Vital Aging Initiative: a private-public partnership to study early predictors of dementia. Alzheimers Dement. 2007; 3:62–7. [PubMed: 19595919]
19. Ferris SH, Aisen PS, Cummings J, Galasko D, Salmon DP, Schneider L, et al. Alzheimer's Disease Cooperative Study Group. ADCS Prevention Instrument Project: overview and initial results. Alzheimer Dis Assoc Disord. 2006; 20(4 Suppl. 3):S109–23. [PubMed: 17135805]
20. Papp KV, Walsh SJ, Snyder PJ. Immediate and delayed effects of cognitive interventions in healthy elderly: a review of current literature and future directions. Alzheimers Dement. 2009; 5:50–60. [PubMed: 19118809]