

Featured Articles

Developing a global strategy to prevent Alzheimer's disease: Leon Thal Symposium 2010

Zaven S. Khachaturian^{a,*}, *Convener–Facilitator*, Ronald C. Petersen^b, Peter J. Snyder^c, Ara S. Khachaturian^d, *Presenters*, Paul Aisen^e, Mony de Leon^f, Barry D. Greenberg^g, Walter Kukull^h, Paul Maruffⁱ, Reisa A. Sperling^j, Yaakov Stern^k, Jacques Touchon^l, Bruno Vellas^m, Sandrine Andrieuⁿ, Michael W. Weiner^o, Maria C. Carrillo^p, *Participants*, and Lisa J. Bain^q, *reporter*

^a*The Campaign to Prevent Alzheimer's Disease by 2020, Rockville, MD, USA*

^b*Mayo Clinic, Rochester, MN, USA*

^c*Lifespan Affiliated Hospitals, Rhode Island Hospital, Providence, RI, USA*

^d*The Campaign to Prevent Alzheimer's Disease by 2020, Washington, DC, USA*

^e*University of California, San Diego, CA, USA*

^f*NYU Langone Medical Center, New York, NY, USA*

^g*Toronto Dementia Research Alliance, Toronto, ON, Canada*

^h*University of Washington, Seattle, WA, USA*

ⁱ*CogState, Melbourne, Australia*

^j*Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

^k*Sergievsky Center and Taub Institute, Columbia University Medical Center, New York, NY, USA*

^l*Hôpital Gui de Chaulliac, Montpellier, France*

^m*Toulouse University Hospital, Toulouse, France*

ⁿ*Department of Internal Medicine and Clinical Gerontology, Acute Unit for Alzheimer's Patients, Toulouse, France*

^o*University of California, San Francisco, CA, USA*

^p*Alzheimer's Association, Chicago, IL, USA*

^q*The Campaign to Prevent Alzheimer's Disease by 2020, Elverson, PA, USA*

Abstract

The fourth Leon Thal Symposium (LTS2010) was convened in Toulouse, France, on November 3, 2010. This symposium reviewed design parameters that are necessary to develop comprehensive national databases on healthy aging. Such datasets offer the potential to serve as the foundation for a *systems-approach* to solve the dual public health problems of: (1) early detection of people who are at elevated risk for Alzheimer's disease, and (2) the development of interventions to delay onset of, or prevent, late-life dementia. The symposium considered three interrelated components of a National Database for Longitudinal Studies on Healthy Aging as follows: (a) a registry of healthy aging adults; (b) refined computer-based assessments for data gathering, including assessments of behavioral/memory changes associated with aging that are appropriate for broad use in nonexpert settings; and (c) high performance computing/supercomputer-based approaches for health data modeling and mining. © 2011 The Alzheimer's Association. All rights reserved.

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1. Background

In the field of therapy development for Alzheimer's disease (AD), a consensus has emerged that the disease must

be stopped in its earliest stages, long before symptoms appear. The ability to reach this objective will require large population-based studies of patients at risk on a global scale.

With this in mind, the fourth Leon Thal Symposium (LTS2010) was convened in Toulouse, France, on November 3, 2010. This symposium was tasked with developing the

*Corresponding author. Tel.: 301-294-7201; Fax: 301-294-7203.

E-mail address: zaven@pad2020.org

parameters for a comprehensive national database on healthy aging, which could serve as the foundation for a systems-approach to solve the dual public health problems of: (1) early detection of people who are at elevated risk for AD, and (2) the development of interventions to delay onset of, or prevent, late-life dementia. The symposium considered three interrelated components of a National Database for Longitudinal Studies on Healthy Aging: (a) a registry of healthy aging adults; (b) refined computer-based assessments for data gathering, including assessments of behavioral and/or memory changes associated with aging that are appropriate for broad use in nonexpert settings; and (c) high performance computing/supercomputer-based approaches for health data modeling and mining.

LTS2010 intended to build on previous Leon Thal symposia, which were established in 2008 to honor the legacy of Leon Thal, who was one of the early proponents of focusing on prevention as the only way to combat the disease. Previous symposia spawned the establishment of a nonprofit organization in the United States called Prevent Alzheimer's Disease by 2020 (PAD2020), which encourages new ways of thinking and new discovery research aimed at developing and implementing a comprehensive plan to achieve the goal of prevention. Recognizing the global effect of AD, the LTS2010 and PAD2020 both have an international perspective, which was reflected in two previous meetings held in Barcelona, Spain, in 2009 [1], and in Jerusalem, Israel, in 2010 [2], which explored the potential for developing collaborative transatlantic longitudinal studies of aging and preclinical and prodromal AD. The meeting in Israel proposed a demonstration project, the Israeli Registry for Alzheimer's Prevention, as a prototype for a comprehensive, international database. In Toulouse, France, participants of LTS2010 focused on identifying the infrastructure needed to bring together and build on existing longitudinal studies as the most efficient means of creating the machinery for conducting large prevention trials.

2. Building on existing registries and longitudinal studies

Developing a worldwide longitudinal database for healthy aging would ideally serve both public health and clinical goals. Indeed, one of the key points of consensus from the symposium is that a transition is needed from the current model of addressing the disease solely through the conduct of clinical trials to a public health model. Thus, a worldwide registry would both gather epidemiologic data that would lead to a better understanding of the natural history of the disease and might also serve as a source of subjects for eventual prevention trials. Moreover, a worldwide registry need not start at the beginning, but rather integrate, coalesce, and expand the existing cohorts that have been established, perhaps by creating a registry of registries that would facilitate a meta-analytic approach to research.

For example, in the United States, the Consortium to Establish a Registry for Alzheimer's Disease was created in 1986 with funding from the National Institute on Aging, and

achieved the goal of developing standardized and validated clinical, neuropsychological, neuropathologic, and behavioral measures for assessing AD [3]. The question now is whether a similar international registry could be created for asymptomatic individuals. Several earlier or ongoing studies that gather data from large cohorts of nondemented individuals serve as models, or possibly the foundation of a more comprehensive global registry. These include the Baltimore Longitudinal Study on Aging, the Rotterdam Study, the Framingham Heart Study, the Alzheimer's Disease Neuroimaging Initiative (ADNI) and its follow-up study, ADNI-II, the Wisconsin Registry for Alzheimer's Prevention, the Mayo Clinic Study of Aging, the NYU Center for Brain Health Study, and the Cardiovascular Health Study, among others. In addition, observational studies have been established in Germany (the German Competence Network on Dementias), Canada (the Canadian Longitudinal Study on Aging [CLSA]), and Australia (Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing); prevention trials have been initiated in France (the Multidomain Alzheimer's Prevention Trial).

In the United States, the Alzheimer's Disease Centers (ADCs) program that was established in 1984, may already provide the basic elements needed for a large international cohort. The ADCs have compiled a huge database of approximately 66,000 subjects enrolled between 1984 and 2005 using the Minimum Data Set. Data from these subjects are included in the National Alzheimer's Coordinating Center at the University of Washington in Seattle. In addition, since 2005, National Alzheimer's Coordinating Center has enrolled some 21,000 subjects assessed with a standardized, clinical evaluation called the Uniform Data Set. These subjects are re-evaluated annually and are almost evenly split between normal cognition, mild cognitive impairment (MCI), and dementia.

Meanwhile in Canada, two population-based studies have been launched, the CLSA and the Ontario Health Study (OHS). CLSA aims to enroll 50,000 subjects between the ages of 45 and 85 years for a minimum of 20 years, collecting information on the changing biological, medical, psychological, social, and economic aspects of peoples' lives, so as to understand how, individually and in combination, these factors have an affect on maintaining health and in the development of age-related disease and disability. The OHS, launched in September 2010, aims to enroll every Ontarian over the age of 18 years—a sampling frame of 9.5 million people—in what could be the largest, transgenerational population-based health study in the world. The OHS will be backed up by some of the best linked administrative health data in the world. One of the advantages of this study is that every time a Canadian uses the Ontarian health system, for example, goes to a healthcare practitioner or hospital, the data are captured, anonymized, and (with careful attention to security and privacy) made available for population-based studies. Although currently in the process of building a stand-alone infrastructure, the OHS group would like to plan obtaining resources that are unique to Canada and synergize with a global effort if feasible.

Designing a worldwide registry may be accomplished most efficiently if built on existing infrastructures such as those that are available in Canada and in some European countries that have electronic medical record systems in place. In the United States, it might be possible to tap into the Department of Veterans Affairs network, which is the largest healthcare system in the United States and one of the largest single-payer systems in the world. The Veterans Administration has had electronic medical record for approximately 20 years, has an aging population, and may also offer advantages in terms of obtaining funding as politicians are sympathetic to veterans' needs. Another opportunity in the United States might be to register people at the time they enter into Medicare, usually at 65 years of age. The new U.S. healthcare legislation requires cognitive screening at the time of enrollment and in subsequent follow-ups.

One of the challenges in using some of the existing cohorts is determining the best way to expand them to include younger individuals. The Mayo Clinic Study, for example, established a population-based cohort of nondemented people between the ages of 70 and 90 years, but to capture presymptomatic individuals, it may be necessary to enroll people in their 60s or even 50s. The NYU Center for Brain Health Study started 15 years ago with normal subjects aged >60 years, and is now enrolling normal individuals aged ≥ 25 years to examine the effects on the brain of a maternal history of AD. Regardless of age, one of the biggest hurdles will be identifying volunteers who are willing to undergo intensive testing repeatedly over 5 to 10 years. An additional issue is how to enroll an unbiased sample. Demographic data from the ADNI study suggest that its participants represent high socioeconomic and highly educated individuals, which may skew the outcomes on the basis of the evidence that these people carry a higher "cognitive reserve" and thus show a pattern of disease progression that differs from that seen in the broader general population.

Another challenge in building a worldwide registry will be to coalesce these efforts underway around the globe without interfering with existing studies. It will also be necessary to address some of the infrastructural barriers to conduct lengthy studies. In the United States, for example, the National Institutes of Health funds projects for a maximum of 5 years, not nearly long enough to conduct the longitudinal studies or prevention trials that are needed. One possible solution to this problem would be the conversion of existing ADCs into Comprehensive ADCs modeled on the National Cancer Institute's Comprehensive Cancer Centers. These centers could provide longer term support, particularly for collaborative projects [4].

3. Worldwide registry—A shared resource to facilitate prevention trials

Although the goal of establishing a worldwide registry would serve the dual purposes of enabling both epidemiologic studies and prevention trials, experience suggests that the populations required for these two kinds of studies are

extremely different. If the purpose of the registry is to feed clinical trials, there should be an effort to enroll subjects who are likely to participate in anticipated trials. But if the purpose is to provide population-based models of the disease, subjects could include those who would not necessarily want to participate in clinical trials. People who participate in clinical trials tend to be more educated, with more resources, higher incomes, and family or primary care physician encouragement to participate [5], whereas people who have fewer resources tend not to enroll in clinical trials.

The ADNI, Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing, and European ADNI are registries established to validate biomarkers for use in clinical trials. ADNI studies, as well as recent work by individual laboratories, suggest that positron emission tomography and magnetic resonance imaging are useful in identifying presymptomatic people with an "AD signature" [6]. Moreover, these studies hint that cerebrospinal fluid (CSF) biomarkers may also be able to identify presymptomatic people with an "AD signature" [7,8], and that subtle cognitive features in the normal range may also be useful markers or indices of disease progression. Indeed, a combination of imaging and CSF biomarkers may be required [9]. ADNI originally focused on the transition between MCI and AD, and ADNI II will enroll additional subjects with very mild or early MCI. A similar registry has been established for conducting clinical trials in France, incorporating 26 regional memory centers.

A possible three-stage model was suggested to achieve the dual goals of establishing a large population-based registry and facilitating clinical trials. In this model, the first level would be a social network similar to *Facebook*. At this level, people would sign up and become part of the network as a means of getting useful information about memory, aging, and AD, but with little asked of the participants in return. Such a network could self-propagate to include hundreds of thousands or even millions of participants. The second level would entail a cohort study built on the network and designed to collect longitudinal information on aging and memory, cognition, and possibly biochemical and imaging markers. The third level would build on level two in designing clinical trials. A similar model has been used successfully in the breast cancer field, allowing rapid recruitment of subjects into clinical trials. The genetics company *23andMe* has also used a similar model, enrolling people who are interested in getting personalized genetics information. However, this model raises many important questions and challenges, including possible bias against older individuals who may be less comfortable with social networking on the Internet.

4. Shifting to a public health model

A different way of conceptualizing the disease will be needed to move toward prevention trials—one that views AD from a public health perspective and uses public health measures to change the course of the disease in the prodromal (preclinical) stage, rather than the traditional model, in

which drugs are used to target a clearly defined biological entity. A public health model deals with large populations and changes that are not easily measurable. Thus, more sensitive functional measures are needed, although it may be necessary to move to using more sensitive cognitive measures or biomarkers because by the time cognitive symptoms manifest, the disease may have already progressed too far for successful intervention.

Many cognitive assessment batteries have been promoted as capable of identifying subtle changes in an otherwise healthy population, although many of them have not supported their claims with adequate validation studies. The ideal battery for use in these large longitudinal studies would function like a thermometer that reliably measures body temperature, that is, by rapidly detecting a *change* in cognitive function regardless of the cause of that change. Thus, the measure has to be stable so that subtle changes can be detected over relatively brief intervals of time; it should have good psychometric properties; it should involve relatively simple tasks; and it should be free of cultural and language biases. Computer-based batteries offer advantages in terms of collecting large amounts of data that may be accessible for decision-making purposes in real time, and they generally are less affected by human administration and data transcription errors. However, the ergonomics of the computer interface need to be simple and easy to train and use with older individuals.

Of the many individual measures that are in wide use at the present time, there are several test paradigms that are increasingly seen as particularly sensitive to the earliest transitional stages from “healthy elderly” to MCI. These include the delayed free-recall measures of word-list learning tests, measures of working memory (e.g., one-back learning tests), and paired associate learning tasks. In all these cases, the actual test or robustness of the paradigm that is most important, rather than the specific sets of stimuli that vary from vendor to vendor. Thus, the selection of a specific test battery for an individual trial may be reasonably based on other important factors, such as cost, availability of well-matched alternate forms, the robustness and reliability of the underlying software platform, HIPAA security, demonstrated adherence to the U.S. Food and Drug Administration (FDA) Code of Federal Regulations Title 21 part 11 regulations, quality assurance issues, rapid availability of quality-checked data, and other practical concerns. Measures that could be adapted to the individual study participant, for example, by comparing each new set of examination results with that particular subject’s running baseline (to detect and monitor within-subject change during a trial), would be a highly desirable “best practice” for the use of computer-based cognitive measures.

These measures may also be useful for selective filtering, in which first a simple test is used to screen a population for people with a slight indication of cognitive impairment, and then additional tests (e.g., biomarkers or genotyping) are used to filter the cohort further and enrich those who are at an elevated risk of decline.

A potential complication regarding the use of cognitive measures in prevention trials is the FDA requirement that changes are clinically meaningful. Thus, it may be necessary to develop functional measures or something else that would be acceptable as a surrogate for clinical relevance and that is appropriate for presymptomatic individuals. A consortium of sponsors has created a workgroup to look at functional changes in early cognitive impairment, possibly even pre-MCI.

Once a set of cognitive measures has been selected, it might be possible to build evaluation of them into ongoing studies such as ADNI and ADCS trials. However, it will be important to see how the instruments perform in the general population first because this could be quite different from how they perform in a clinical trial population. It would also be helpful to correlate these measures with the presence of amyloid in the brain. In addition, as part of the general research agenda, there should be a continuing search for measures that are more sensitive to change in the preclinical population. Research in the basic science of cognition has uncovered many sensitive paradigms that have not been capitalized on with regard to test development, but that may be exquisitely sensitive to changes in the biology of AD long before there are symptoms. For example, a change in the variability of performance on certain measures could potentially be a very rich area.

5. Barriers and solutions to prevention trials

There are numerous other barriers that need to be addressed if large population-based prevention trials are to be conducted successfully. With current technologies and the existing regulatory policies, prevention trials would take an unacceptably long period.

Regulators will need to accept a change in slope as an outcome measure. A willingness to accept such secondary measures has been indicated. Researchers need to accumulate data that robustly link change in biomarkers to eventual change in clinical status, so that disease progression can be monitored before the emergence of clinical symptoms.

In addition, pharmaceutical companies will require more of an incentive than a 3-year extension of exclusivity before they will be fiscally able to undertake development of a preventive treatment. But a change in patent law alone will probably not be enough; there are also commercial boundaries that need to be overcome. To provide a drug to people who have no signs of disease (i.e., preclinical AD), the drug must meet a high safety barrier, but this is generally not considered to have been met before the patent on the drug has expired. The question is how can you commercialize something that is in the generic world?

Reliable genetic markers and/or tests that would identify with great accuracy asymptomatic people at elevated risk in preclinical stages of the disease are urgently needed for the design of future prevention trials. Although substantial progress has been made identifying genes for early-onset AD, the more common late-onset form of the disease has

been more difficult to solve. Until recently, the only confirmed susceptibility locus for the sporadic form of the disease was apolipoprotein $\epsilon 4$ (*APOE* $\epsilon 4$). Now, the combination of high-density genotyping methods, applied to large cohorts of well-characterized people with the disease and control populations, as well as novel statistical methods to evaluate population stratification, has begun to provide the tools to identify additional genes that might contribute to an elevated risk of AD. In large multisite genome-wide association studies involving 7070 cases with AD, 3055 with autopsies; and 8169 elderly cognitively normal controls, 1092 with autopsies, Jun et al have found evidence that variations in encoding clusterin, encoding the phosphatidylinositol binding clathrin assembly protein (PICALM), and encoding complement component [3b/4b] receptor 1 confer genetic risk for AD. Genotypes at PICALM confer risk predominantly in *APOE* positive subjects. Thus, *APOE* and PICALM interact synergistically [10].

One approach to drug development that may advance this process is to establish noninvasive markers of risk, including but not necessarily limited to genetic tests. One illustrative example of this is the proposal to use a genetic factor such as TOMM40, which could be used to stratify people into high- or low-risk of developing dementia within 5 years [11]. The FDA has accepted a proposal for a trial design that combines (1) confirmation of the clinical characteristics and accuracy of prediction for the genetic test, and (2) evaluation of the effectiveness of a drug in delaying onset in a high-risk group identified by the genetic test. An investigational new drug application is being submitted as a demonstration trial entitled “Opportunity to Prevent Alzheimer’s - OPAL.”

One concern raised by such a design is the question of whether it will enrich the trial cohort in a manner that would be generalizable to the entire population. Indeed, all clinical trials that run through ADCs have this problem because studies have shown that in the general population, about 35% of people carry the *APOE* gene (a risk factor for AD), as compared with about 55% in the ADCS population. To the extent that *APOE* co-segregates with a biological cause of AD, for example, amyloid processing, a drug that targets amyloid might perform differently in the general population than in the clinical trial population.

Not all biomarkers are likely to serve as strong predictors or indicators of disease progression at any given stage of the disease. For example, the specific markers for amyloid and tau may not show progression, whereas some of the nonspecific biomarkers (e.g., fludeoxyglucose [18F]-positron emission tomography, magnetic resonance imaging, and CSF isoprostane) might be more useful indicators of progression at a certain stage of the neurodegenerative process. This indicates the need for developing a model for “layering” various biomarkers and algorithms for interpreting the patterns of changes in the surrogates for disease progression.

Ethical issues also need to be addressed in designing prevention trials based on population studies and registries. Typically, participants are anonymized during the data collec-

tion phase. However, a consent could perhaps be created based on the concept that AD is a heterogeneous set of entities, which would allow for de-anonymizing individuals who might be responsive to specific therapies that will be developed in the future by the pharmaceutical and biotechnological industries so that these individuals could be enrolled in controlled studies to demonstrate a signal at a particular therapeutic target.

Another hurdle that will have to be addressed in prevention trials relates to risk–benefit perception. The concept of the risk–benefit ratio of a treatment is more palatable in a group of people known to be at higher risk of disease than in the general population. Giving asymptomatic people a drug that carries any sort of risk with it, or getting payers to pay for such treatment, is likely to be problematic.

6. Computational modeling and data analysis

Perhaps the most critical barrier to therapy development is the lack of modeling systems that simulate the entire spectrum of clinical phenotypes. Although traditional modeling systems (specifically, *in vitro*—[cell cultures] and *in vivo* [transgenic or other animal models]) are available, these models do not show the complete range of biological and clinical features of human disease. A key limitation of these models is the inherent inability to provide insight into the precise functional relationships between the clinical (symptomatic) and biological (neurobiological marker) phenotypes. As a result, the discovery of a biological marker for a disease or the identification of a molecular target often does not translate into an effective therapy. The nonlinear relationship between molecular events and clinical symptoms remains a major challenge for therapy development.

The emergence of *in silico* modeling systems, particularly the class of modeling generally referred to as multimodeling approaches, may add an important new tool for investigators. These methods offer the unique possibility to understand the relationship between molecular phenomenon in the neuron and the emergent behavior as clinical symptoms of the whole complex system.

A necessary component for a database that can serve the needs of a multidisciplinary research community is the infrastructure to support the development of computer modeling approaches (model-bases) and databases. Thus, PAD2020 has been working with the University of Nevada, Las Vegas Supercomputing Center, to establish a National Neuroscience Numerical Laboratory (3NL).

The 3NL will serve as a neuroscience information management system. The project will create a highly integrated user-friendly tool to enable generation of new hypotheses and multidisciplinary *in silico* experiments, and the harmonization of different types of information (e.g., clinical, imaging, genetic, neuropsychological, and biological). Fortunately, the effort to establish such a critical research infrastructure will not be difficult because several *in silico* modeling systems, databases, and other important components exist.

The 3NL will provide a shared high-performance computing research infrastructure based on “grid” and “grid cluster” technology. High-performance computing generally implies a system (or array) of machines capable of storing large datasets and performing calculations at a high rate. (The word “grid” conveys the analogy to an electrical power grid, which provides pervasive, dependable, consistent, and inexpensive access to advance resources.) Ultimately, researchers will be unaware that they are using any computer other than the one on their desk, because it will have the capability to reach out across the national network and obtain needed data, analytical assays, and/or computational resources.

The idea of applying supercomputing resources to biomedical problems is one of the “Grand Challenges” identified in the late 1980s by the U.S. government; the idea being that many researchers would deposit data into this system, which would allow simulations of various diseases. 3NL is envisioned as a resource available to the entire research community, which would support ongoing studies with data management and data mining and apply a systems biology approach to develop a better understanding of the physiology of disease progression and identify biomarkers that are most meaningful. Supercomputing capabilities could be especially useful in performing factor analysis in a registry of registries, and in detecting small changes in continuous data gathered from home-based systems. One concern about such a system is whether investigators would be willing to co-locate their data or have data collected and stored exclusively at 3NL supercomputer. It will also be critical to establish detailed protocols for collection and cleaning of data.

Currently, the PAD2020 plan is to bring computational biology experts together with investigators from across many domains who have a good understanding of the disease process. The complexities of this system are enormous, but there exist examples from other areas (e.g., weather modeling and hurricane prediction) that show it is possible to develop models for dealing with very complex data.

7. Conclusions and future plans

Consensus continues to build on the need to launch an integrated worldwide effort to prevent AD starting with a worldwide registry of individuals willing to participate in longitudinal studies of aging. As individual countries

move forward with plans to establish registries, it will be important to continue the dialogue that has been facilitated through the LTS2010 so that these various studies can both maintain their autonomy and become integrated into a global endeavor. This ongoing dialogue must address the need to develop common tools and build an infrastructure that is adaptable to the various economic, political, and public health institutions in participating countries, including countries that have not yet launched major AD initiatives.

References

- [1] Khachaturian ZS, Camí J, Andrieu S, Avila J, Boada Rovira M, Breteler M, Froelich L, et al. Creating a transatlantic research enterprise for preventing Alzheimer's disease. *Alzheimers Dement* 2009;5:361–6.
- [2] Khachaturian AS, Chapman J, Farrer L, Friedland RP, Ebstain R, Grossman I, et al. Healthy aging and preclinical dementia: the United States-Israeli Longitudinal Database Project. *Alzheimers Dement* 2010;6:475–81.
- [3] Fillenbaum GG, van Belle G, Morris JC, Mohs RC, Mirra SS, Davis PC, et al. Consortium to Establish a Registry for Alzheimer's Disease (CERAD): the first twenty years. *Alzheimers Dement* 2008;4:96–109.
- [4] Trojanowski JQ, Arnold SE, Karlawish JH, Brunden K, Cary M, Davatzikos C, et al. Design of comprehensive Alzheimer's disease centers to address unmet national needs. *Alzheimers Dement* 2010;6:150–5.
- [5] 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.
- [6] Mosconi L, Berti V, Glodzik L, Pupi A, De Santi S, de Leon MJ. Pre-clinical detection of Alzheimer's disease using FDG-PET, with or without amyloid imaging. *J Alzheimers Dis* 2010;20:843–54.
- [7] Brys M, Pirraglia E, Rich K, Rolstad S, Mosconi L, Switalski R, et al. Prediction and longitudinal study of CSF biomarkers in mild cognitive impairment. *Neurobiol Aging* 2009;30:682–90.
- [8] De Meyer G, Shapiro F, Vanderstichele H, Vanmechelen E, Engelborghs S, De Deyn PP, et al. Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. *Arch Neurol* 2010;67:949–56.
- [9] de Leon MJ, Mosconi L, Blennow K, DeSanti S, Zinkowski R, Mehta PD, et al. Imaging and CSF studies in the preclinical diagnosis of Alzheimer's disease. *Ann N Y Acad Sci* 2007;1097:114–45.
- [10] Jun G, Naj AC, Beecham GW, Wang L-S, Buros J, Gallins PJ, et al. Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. *Arch Neurol* 2010;67:1473–84.
- [11] Roses AD. An inherited variable poly-T repeat genotype in TOMM40 in Alzheimer disease. *Arch Neurol* 2010;67:536–41.