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The Alzheimer's Disease Neuroimaging Initiative: Progress report and future plans

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Abstract

The Alzheimer's Disease Neuroimaging Initiative (ADNI) beginning in October 2004, is a 6-year re-search project that studies changes of cognition, function, brain structure and function, and biomarkers in elderly controls, subjects with mild cognitive impairment, and subjects with Alzheimer's disease (AD). A major goal is to determine and validate MRI, PET images, and cerebrospinal fluid (CSF)/blood biomarkers as predictors and outcomes for use in clinical trials of

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AD treatments. Structural MRI, FDG PET, C-11 Pittsburgh compound B (PIB) PET, CSF measurements of amyloid β (Aβ) and species of tau, with clinical/cognitive measurements were performed on elderly controls, subjects with mild cognitive impairment, and subjects with AD. Structural MRI shows high rates of brain atrophy, and has high statistical power for determining treatment effects. FDG PET, C-11 Pittsburgh compound B PET, and CSF measurements of Aβ and tau were significant predictors of cognitive decline and brain atrophy. All data are available at UCLA/LONI/ADNI, without embargo. ADNI-like projects started in Australia, Europe, Japan, and Korea. ADNI provides significant new information concerning the progression of AD.

Keywords

ADNI; Alzheimer's disease; MRI; PET; Amyloid; Memory; Tau

1. Introduction

1.1. Historical background and rationale for ADNI

Alzheimer's disease currently affects more than five million patients in the U.S. and will rise to 16 million by 2050 [1], costing the U.S. economy more than $140 billion/yr [1,2]. Globally, an estimated 35.6 million people have dementia (largely because of AD), which is expected to reach 65.7 million in 2030 and 115.4 million in 2050 [3]. It is generally accepted that there is a pressing need to develop effective disease-modifying treatments to slow or halt progression of AD pathology to be used in subjects with dementia, mild cognitive impairment (MCI), and in control subjects at risk for development of cognitive decline and dementia. Presently, no treatments have been convincingly demonstrated to slow the progression of AD pathology.

The historical background to Alzheimer's Disease Neuroimaging Initiative (ADNI) is a long and complex story, best summarized in Reference [4]. Because AD is a disorder which affects cognition (especially memory) and leads to dementia, for many years a major focus was the behavioral characterization of the disorder including the development of standardized methods for assessment, diagnosis, and monitoring of progression of clinical symptoms and impairments. The recognition that AD dementia slowly develops as part of a spectrum from normal aging to MCI sprang out of the clinical and behavioral context. At the same time, for the past 20–30 years, a number of biological methods have been increasingly used to obtain quantitative information concerning changes in the brain and in biological fluids which occur in AD. Most notably, the development of FDG PET and MRI in the 1970s has led to an increasingly large body of knowledge about the changes in AD. Furthermore, changes in cerebrospinal fluid (CSF) proteins, notably abeta and tau, have also been studied for many years. One important highlight in the use of biomarkers was an National Institutes of Health (NIH) conference in 2000, organized by Dr Neil Buckholz, concerning the use of Biomarkers in AD. Shortly thereafter, the Alzheimer's Imaging Consortium was established as a forum for discussion and exchange of ideas and information concerning using MRI and PET to study AD. In summary, during the 1980s and particularly the 1990s, there was increasing research activity using a wide variety of biomarkers, especially MRI, FDG PET, and measurements of CSF to study this disorder. Many investigators were reporting studies using different methods on different cohorts of subjects. Thus, it was somewhat difficult to compare the value of all these different methods. The need to develop a large cohort, in which the methods could be compared, became increasingly obvious to all in the field.

The original impetus for the ADNI began around 2000, when it was observed that many academic investigators, pharmaceutical companies, and biotech companies were beginning

to develop treatments aimed at slowing the progression of AD. Measurements of cognition or conversion from MCI (generally accepted as a precursor to dementia) to dementia could not in themselves demonstrate that the treatments were slowing disease progression, because impaired cognition in AD and MCI can be improved with symptomatic treatments such as acetylcholinesterase inhibitors. Additionally, in 2000, there were insufficient standards for obtaining or measuring imaging and/or biomarkers for AD for the numerous investigators who were studying disease progression by measuring various imaging and CSF/blood biomarkers. Also lacking at the time was sufficient data to determine the relative value of biomarker measures to detect progression of AD in treatment trials. A comprehensive understanding of the sequence of pathophysiological events that cause AD and lead to dementia at the molecular, cellular, brain, and clinical levels was clearly needed. In addition, measurements that identify the various elements and the factors that influence AD pathology in living human subjects needed to be developed for use in early diagnosis and as risk factors and/or predictors for cognitive decline or dementia. Such measurements could eventually have utility in clinical trials and practice and thus support the ultimate goal of AD research to develop treatments that can slow the progression of AD and ultimately prevent the development of AD (either secondary, prevention, or primary prevention).

1.2. Disease model

ADNI research is based on a model (Fig. 1) positing that AD begins with Aβ accumulation in the brain, which ultimately leads to synaptic dysfunction, neurodegeneration, and cognitive or functional decline. This predicts that the earliest detectable changes (measured in the ADNI project) are those related to Aβ (detected in CSF and by PET amyloid imaging). Subsequently, neurodegeneration is detected by a rise of CSF tau species, synaptic dysfunction (measured by FDG-PET), and neuron loss indicated by atrophy, most notably in medial temporal lobe (measured with MRI). The temporal sequence of changes in Aβ deposition, CSF tau species, and imaging using FDG-PET and MRI remains to be determined. These changes ultimately lead to memory loss, general cognitive decline, and eventually dementia. Expression of each element of AD pathology (e.g., Aβ and tau deposits, atrophy) is influenced by many modifying factors including age, *APOE* genotype, and cerebrovascular disease (white matter lesions detected by fluid attenuated recovery [FLAIR MRI]) and microbleeds (detected by T2* MRI), and there are expected to be wide differences among individuals.

Although this simple model does not convey the complexities of the relationships among aging, tau phosphorylation and conformational change, amyloid peptide accumulation and conformational change, synaptic dysfunction and neuronal loss, we believe it is useful for the interpretation of biomarker, cognitive and clinical data from ADNI and other studies, and in the incorporation of biomarker measures into trial designs.

The ADNI project, however, is not built around, and does not depend on, the amyloid hypothesis. Despite the evidence in favor of this hypothesis [5], other evidence does not necessarily support all aspects of it. For example, the early Braak stage consists of tau tangles and synapse loss in the entorhinal cortex and hippocampus without amyloid accumulation [6–8]. In addition, there is poor correlation between brain amyloid level and cognitive impairment. A follow-up study of subjects in the Wyeth Elan 1792 vaccine trial showed amyloid removal (at pathology) in some subjects, while they continued to decline cognitively [9]. One possibility is that subjects with dementia have such severe brain damage that amyloid removal does not slow progression of symptoms. However, the failure of anti-amyloid clinical trials could be due to many reasons, including the possibility that the treatments did not sufficiently reduce brain amyloid. In possible support of this model, it has been recently reported (in one subject) that CSF amyloid falls before development of C-11 Pittsburgh compound B (PIB) positivity, which precedes cognitive impairment [10].

Replication and extension of this sequence of events in a multisite study with large sample size will provide critical information concerning the neuroscience of AD.

An important point to emphasize is that we have limited information concerning the pathophysiological sequence of events of AD in human beings from autopsy studies and from studies measuring only cognition. Our model suggests that different imaging modalities, measurements, and different biochemical markers will usefully serve as predictors (measurements which predict future change) and outcomes (measurements that detect change) at different stages in the transition from normal aging, to MCI, to dementia. Furthermore, the model suggests that the measurements most likely to predict decline in normal subjects will be the detection of Aβ in CSF, using PET perhaps in combination with measurements of CSF tau species, the use of brain imaging by FDG-PET, and MRI. Although amyloid biomarkers may be useful predictors of decline in early MCI (EMCI), CSF tau measurements, FDG-PET, and MRI measures of regional atrophy, which likely change after amyloid markers change, may be more predictive. In late MCI (LMCI) and AD, we hypothesize that the most effective biomarkers for prediction of further decline will be FDG-PET, MRI, and cognition. Biomarkers that are most likely to correlate with, and augment the utility of, cognitive and clinical measures as outcomes in clinical trials are FDG-PET, possibly MRI measures of volume (especially of hippocampus and temporal cortex) at early stages, and atrophy throughout the brain at later stages. However, it is recognized that the performance of the various imaging and CSF/blood measurements depends both on the biological sequence of events as well as the sensitivity, accuracy, and precision of the various measurements. Thus, for example, a test which best predicts future cognitive decline in normal subjects may not necessarily represent the earliest biological change, but rather the earliest change that is detected by a sensitive and robust test.

1.3. Goals of ADNI

The overarching goals of ADNI, therefore, were to determine the relationships among the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics of the entire spectrum of AD as the pathology evolves from normal aging through very mild symptoms, to MCI, to dementia, and to establish standardized methods for imaging/biomarker collection and analysis for ultimate use in clinical trials.

Initially, ADNI primarily aimed to ascertain the relative value of various imaging, and CSF/blood biomarkers as *outcome* measures in trials of AD and MCI subjects. Specific goals to this end included the validation of MRI and PET imaging, and of blood and CSF biomarker measures by examining their relationships with cognitive and functional measures, the identification of the most effective measures for monitoring treatment effects in different stages in the progression of normal aging, through MCI to AD, and the development of statistical models of cross-sectional and longitudinal clinical, imaging, and biomarker data, which could be used for future hypothesis generation and testing. Other goals of ADNI were to develop improved standardized methods for performing AD trials by creating uniform standards for MRI and PET acquisition, to develop improved methods of acquiring and processing multisite longitudinal data that would increase cost-effectiveness and power of future treatment trials, and to develop statistical models of cross-sectional and longitudinal clinical, imaging, and biomarker data that could be used for future hypothesis generation and testing. Finally, ADNI aimed to create a data repository for academics and industry for a multiplicity of purposes. This repository would provide further information regarding longitudinal changes in brain structure, function, cognition, blood, urine, and CSF biomarkers that occur in normal aging, MCI, and AD as well as transitions from one of these states to another. Data generated by ADNI would be available to qualified scientists worldwide without embargo.

In the 5 years since the funding of ADNI in 2004, there has been increased interest in the use of imaging and CSF/blood biomarkers to identify AD pathology in subjects before dementia, and to develop diagnostic criteria that use these measurements [11]. Data from ADNI have proved to be a valuable resource to address these issues, and thus the development of imaging and CSF/blood biomarkers as predictors has become an important goal of ADNI.

1.4. Identification of outcomes and predictors

Different biomarkers will be effective *predictors* of cognitive decline or dementia or *outcomes* (measures of change) at different stages across the continuum from normal cognition to AD dementia. Understanding the sequential change of biomarkers and their relative value as predictors and outcomes at the presymptomatic, mild symptoms or MCIs, and dementia stages of the disease is crucial to understanding the neuroscience of AD, and may lead to improved diagnostic tests and facilitate design and power calculations of clinical trials for disease-modifying agents.

Measures of rates of change serve as *outcomes* in clinical trials. A problem with AD clinical trials is the length of time and large sample sizes required because of the high variability of clinical and cognitive measures. Numerous reports suggested that changes in brain structure (detected by MRI) or brain glucose metabolism (detected by FDG-PET) had higher statistical power to detect change than clinical or cognitive measures because of their low variability. Interest in biomarkers was further increased because measures of function and cognition are affected by many things (e.g., depression, other illnesses) in addition to features of AD, are potentially affected by drugs such as cognitive enhancers, have low statistical power to determine effects of disease-modifying treatments, and only indirectly reflect disease progression.

Furthermore, biomarkers that directly or indirectly measure AD pathology may be used as *predictors* of cognitive decline or dementia. Such predictors will assist in the enrichment and selection of subjects with mild impairment and in normal elderly subjects for treatment trials and even prevention trials. It is generally accepted that AD pathology (amyloid plaques, tau tangles, synapse loss, gross neuron loss, and brain shrinkage) begins many years before dementia and often exists with no evidence of cognitive impairment. The cognitive impairment caused by AD pathology is thought to occur within the context of the cognitive changes which occur in normal aging, and is characterized initially by problems with memory functioning. This progresses to deficits in other cognitive domains, functional abilities, and frank dementia. Evidence exists that the pathological and cognitive changes are nonlinear in that there is a gradual acceleration of pathological and cognitive changes. There is a compelling need to identify measurements that identify the presence and extent of AD pathology in the living brain, thus characterizing the stage of disease. Because of the nonlinear nature of the process, knowledge of the stage of progression could potentially be used to predict the future rate of cognitive decline and the future occurrence of dementia (the more advanced the progression, the greater the rate of future change). As amyloid plaques develop, considerable evidence suggests that CSF Aβ amyloid decreases [12,13]. Thus, CSF Aβ is a putative measure of brain amyloid deposition. Brain amyloid is directly detected by PET amyloid ligands. CSF tau increases in the progression of controls to MCI to AD [12,13], and is a putative measure of the deposition of tau tangles and neurodegeneration. No direct measures of brain synaptic density exist in human beings, but brain activity is reduced as synaptic density falls, and FDG-PET is a quantitative measure of brain activity that appears to identify early AD. Structural MRI detects brain atrophy, and hippocampal volume shrinkage has been correlated with neuronal loss [14] and neurofibrillary tangles. Thus, each of these measures has predictive value, but their relative values at the different stages across the continuum have not been established. Several investigators have proposed that imaging and CSF biomarkers could be used to identify AD pathology in subjects who

are not demented, and could thus be used for diagnosis of AD [11]. Several pharmaceutical companies and the Alzheimer's Disease Cooperative Study (ADCS) have proposed performing AD treatment studies using subjects with early AD, meaning nondemented subjects with cognitive impairments who have imaging/CSF biomarker evidence of AD pathology (especially low CSF Aβ and/or C-11 PIB positivity), but the value of this approach has not been established. Genetics may also be considered a predictor in AD. ADNI included analysis of the *APOE* ε4 gene during enrolment to balance the frequency of this gene in the PET and CSF sub-studies. Subsequently, a genome-wide association analysis was performed on the DNA of all ADNI subjects.

2. Methods

2.1. ADNI structure and organization

ADNI is structured as eight cores under the auspices of the Administrative Core, directed by Dr Weiner, the principle Investigator. ADNI is a U01 cooperative agreement grant, and the NIA requires that this project be governed by a Steering Committee consisting of Dr Weiner and all funded Core leaders, all Site Principal Investigators, representatives from the NIH and US Food and Drug Administration (FDA), and representatives from each of the contributing companies as observers only. The day to day decisions are made by the ADNI Executive Committee (Excom) which includes the Principal Investigator, the Core leaders, a representative of the NIA (Dr Buckholtz), the current, past, and future Chairs of the Industry Scientific Advisory Board (ISAB; as observers), and David Lee of the Foundation for the NIH (as an observer). The governance and organization of ADNI are depicted in Fig. 2.

The original cooperative agreement (U01) grant, termed ADNI1, was funded as a public/private partnership with $40 million from NIA and $20 million from 13 companies in the pharmaceutical industry and two Foundations, for a total of $60 million. Since then, additional companies have joined, bringing the total to 22. An additional $7 million has been provided in the form of supplements for (1) the C-11 PIB sub-study; (2) the lumbar puncture extension (beyond the original 1 year of funding); and (3) the genome-wide association analysis of the DNA of all ADNI subjects. All funds from industry are provided to the Foundation for NIH which then provides the combined funds to NIA who awards funds in the form of a UO1 grant to ADNI. (Table 1).

All sites are managed by the ADNI Clinical Core at the ADCS, University of California, San Diego (Paul Aisen, PI). The Data and Publications Committee (DPC) vets all publications using ADNI data (see description in the supplemental references, online only). The ISAB is composed of representatives from all companies which provide funds to ADNI and is managed by the Foundation for NIH. The ISAB is chaired on a rotating basis. Chairs have included William Potter (Merck 2005, 2006), Eric Siemers (Lilly, 2007), Patricia Cole (Eisai, 2008), Holly Soares (Pfizer, 2009), and in 2010 Mark Schmidt (Novartis).

The Scientific Advisory Board is Chaired by Zaven Khachaturian, meets annually, and has consisted of many prominent physicians and scientists including Lewis Kuller, Dennis Choi, Gregory Sorensen, Peter Snyder, William Thies, Howard Fillit, William Friedewald, Richard Frank, Richard Frakowiack, and Thomas Budinger.

All requests for specimens (blood, plasma, CSF, DNA, immortalized cell lines) go directly to the Resource Allocation Review Committee (RARC), consisting of members independent of ADNI, approved by the NIA, and chaired by Dr Tom Montine at the University of Washington, Seattle, Washington. After approval by the RARC, the NIA must approve release of all specimens.

2.1.1. Administrative core—The Administrative Core is located at the San Francisco VA Medical Center/University of California, San Francisco/NCIRE. It consists of the Principal Investigator of ADNI (M.W. Weiner), his administrative staff, statistical support, and the DPC administered by Robert Green at Boston University. Dr Weiner has responsibility for all administrative, financial, and scientific aspects of ADNI. In addition to the highly complex administration of grant finances, some image analysis of ADNI data, using FreeSurfer (from Massachusetts General Hospital, Bruce Fischl, PI) is performed at the San Francisco, VA, overseen by Dr Schuff. This work is part of the MRI Core (Fig. 3).

2.1.2. Data and publications committee (DPC: PI Robert Green)—The DPC performs three tasks: (1) It develops and proposes policy to the Executive and Steering Committees regarding data access and publication; (2) It screens all applications for access to ADNI data; and (3) It reviews all publications for adherence to ADNI publication policy guidelines. The DPC helped develop policies for open data access such that virtually all requests for data access are granted. Persons requesting access to the data fill out a brief online application form in which they indicate their academic affiliation and reason for requesting access, or a statement about the project area they are interested in. Each of these applications is individually reviewed by the DPC Chair. A table of individuals with access to the data and the projects they are pursuing is publically available so that data users can be aware of the interests of others and reach out to other data users to form collaborations if they wish. The DPC Administrator reviews manuscripts and requires all scientists who are developing manuscripts using ADNI data to adhere to ADNI publication guidelines. These guidelines request that authorship be stated in the “modified corporate authorship” format, in which the particular writing team is named, and the authorship list is followed by the words, “for the ADNI Study*”; the asterisk here refers to a web page where the ADNI leadership and individual site directors and co-investigators at each ADNI site are named. In this manner, the ADNI leadership and ADNI site investigators can obtain group authorship credit that provides at least modest academic credit for the work they are doing toward all ADNI publications.

A member of the DPC also reviews each manuscript for any that may have egregiously poor quality, but importantly, does not attempt to review manuscripts for scientific quality or for duplication. It has been our conscious policy to avoid practices that would inhibit or slow the utilization of ADNI data by the worldwide scientific community. Therefore, we have decided that scientific review should occur at the level of publication review, and that we will tolerate, and even encourage, multiple examinations of ADNI data by multiple investigators. Although this philosophy raises the possibility that two papers could present conflicting analyses or interpretations, we have elected to let such potential conflicts play out in the marketplace of ideas.

2.1.3. Other cores—Briefly, the eight cores for which the administrative core is responsible are as follows: (1) Clinical Core, based at the University of California, San Diego, and the Mayo Clinic, and is responsible for the recruitment of subjects, the development of an electronic data capture system at each site, and of protocols and procedures for ADNI; (2) MRI Core, based at the Mayo Clinic, and responsible for all MRI procedures and for developing standardized imaging methods; (3) PET Core, based at the University of California, Berkeley, and responsible for all PET procedures and for developing standardized imaging methods; (4) Biomarker Core, based at the University of Pennsylvania, and responsible for the collection and analysis of biomarkers in biofluids, and for the establishment of an archive of biofluids; (5) Genetics Core, based at Indiana University and responsible for genotyping participants; (6) Neuropathology Core, based at Washington University, and responsible for the establishment of protocols to facilitate brain autopsies of ADNI patients who die; (7) Biostatistics Core, based at the University of

California, Davis, and responsible for the statistical analysis of data generated from the other Cores; (8) Informatics Core, based at the University of California, Los Angeles, and responsible for the establishment of a website to facilitate data-sharing of data generated by ADNI projects.

Detailed summaries of the results of the ADNI Cores are provided in the accompanying articles of this special issue.

3. Limitations of ADNI

One limitation of ADNI is that our population represents a clinical trial population and not an epidemiologically selected real life population. Our subjects do not include those with cortical strokes, cancer, heart failure, substance abuse, etc. Therefore, the extent to which the results from ADNI can be generalized to the entire population remains to be determined. Future population-based studies will be required to determine whether the information derived from ADNI is relevant to the greater population. One approach has been for ADNI investigators to develop collaborations with investigators who are conducting population-based studies, so that ADNI methods can be used in such studies. A second limitation is that ADNI only studies subjects aged 55–90 years, and there is considerable evidence that AD pathology may begin to occur in the human brain well before this age. Autopsy studies and amyloid imaging have suggested that a substantial fraction of cognitively normal subjects in their 70s have AD pathology. A full understanding of the pathophysiological sequence of events that occur in AD will require longitudinal studies of subjects beginning at a young age. A third limitation of ADNI is the type of data that are not being collected including computerized neuropsychological testing, electroencephalogram, magnetoencephalography, magnetic resonance spectroscopy, metabolic and inflammatory markers, and lifestyle information. The decision concerning which measures to include was reached by consensus among the Site Principal Investigators (PIs), Core leaders, and the NIA. Although many of these measures might provide useful information, they are not included because of the following reasons: (1) The measures have not yet been demonstrated to have high value as either predictors or outcomes, and are not currently being incorporated into clinical trials; (2) The subject burden of ADNI is already quite great (clinical/cognitive battery, MRI, FDG/amyloid PET, lumbar puncture) and there are concerns that adding additional tests will impair enrollment and increase dropout; (3) The additional cost of these measures is not supported by evidence for inclusion. One final limitation of ADNI has been that not all measurements (like FDG-PET and lumbar puncture) were obtained on all subjects, limiting the ability to compare methods. This is being overcome in the current study in which all subjects will have (at least) baseline lumbar puncture and AV-45 amyloid imaging as well as the other measurements.

4. Results

4.1. Overall ADNI impact

The effect of ADNI thus far falls into three main areas. First, the establishment of standardized methods for imaging/biomarker collection and analysis has been a key step forward, and these methods are starting to be used in clinical trials. For instance, ADNI results on LMCI subjects replicated rates of conversion in a similar group of MCI subjects enrolled using the Petersen criteria in the ADCS Vitamin E/Donepezil trial, and the standardized neuropsychological battery used by ADNI is now being used by industry and ADCS trials. The MRI core developed a structural MRI protocol, identical across vendors, with an MRI phantom for calibration which has since been used in numerous phase 2 and 3 treatment trials. The PET core established methods for multisite FDG-PET, and the first multisite C-11 PIB study. The biomarker core established standardized methods for

measurements of CSF Aβ amyloid and species of tau. The importance of these standardization efforts should not be underemphasized because the ADNI methods have now been adopted for other ADNI-like studies outside of the U.S. and this will facilitate comparisons of results among countries, cultures, and ethnicities, and provide an infrastructure for worldwide clinical trials by the pharmaceutical industry. Second, ADNI has resulted in the provision of a large data base of images, genetic, fluid biomarker, and clinical data that are being used by many investigators and industry. Finally, ADNI has generated new results in many areas, such as the identification of outcome measures with high power to detect treatment effects, and of predictors such as CSF biomarkers which have been shown to predict future rates of brain atrophy, brain glucose metabolism, and cognition in MCI. Contributing to the knowledge of AD neuroscience is the finding that there is evidence that AD pathology in normal subjects is associated with greater rates of change of brain structure and brain glucose metabolism. Amyloid imaging and CSF Aβ have been found to provide similar information. An important long-term goal of our field is to identify and validate imaging/biomarkers for AD progression which can be used as surrogate markers in place of clinical/cognitive tests in clinical trials. This is a very long way off, because such surrogate markers must be validated in the treatment setting, across various types of treatments. Nevertheless, the ADNI results are providing an important first step toward this goal.

ADNI has also had a great effect in a global sense (Fig. 4). At the time when ADNI1 was funded, there were no plans for similar efforts in other countries. However, the establishment of ADNI stimulated many such efforts resulting in the following: (1) The Australian study, AIBL (PI Colin Masters) [15], is a two-site longitudinal study of 1,100 subjects with MRI (using ADNI protocol), a subset with C-11 PIB, and cognitive measures (similar to ADNI). In fact, AIBL was conceived of before and began independent of U.S. ADNI; (2) Japanese ADNI (PI Takeshi Iwatsubo) [16], which studies 220 subjects using methods identical to ADNI in all respects except for language; (3) European ADNI (PI Giovanni Frisoni), which is enrolling 150 subjects. There are also several large longitudinal projects beginning in China using imaging/CSF biomarkers and a Korean ADNI is being planned. The Alzheimer's Association has organized a quarterly teleconference of all worldwide ADNI PIs, is working to fund more data-sharing efforts among the projects, and Dr Iwatsubo hosted the first worldwide ADNI meeting in Sendai, Japan, in November, 2009.

Thus, the effect of ADNI and these numerous projects around the world on AD research is huge, as is the value of the information gained to academic scientists and to the pharmaceutical industry as a result of the sharing of all data. To our knowledge, ADNI is the only neuroscience project in the world that is having such a worldwide effect in the AD field. To date, there have been more than 60 publications arising from AD, both directly, or indirectly through shared data (Appendix list, online only).

4.2. Grand opportunities grant

A Grand Opportunities (GO) grant (American Recovery Act funds, i.e., stimulus funds) was recently awarded to the identical team of investigators overseeing ADNI. Dr Weiner is also PI of the GO grant, which closely relates to ADNI and is separately administered with its own account/fund and separate subcontracts. This grant will provide an additional $24 million of funding over 2 years to enroll 200 EMCI subjects, some of whom will have early biomarker signals of AD pathology. This category of subjects has not been enrolled in ADNI thus far, and so it will bridge the gap between normal elderly and LMCI subjects who are more amnestic than EMCI subjects. These GO subjects will have clinical/cognitive, blood/CSF/genetic, FDG and amyloid PET, and MRI measurements during the 2-year period of the GO grant. This grant will also fund F18 amyloid PET imaging on all existing normal control and LMCI subjects, and newly enrolled EMCI subjects, which will allow

correlation and comparison of this modality with all of the other clinical/cognitive, neuroimaging, genetic, and biomarker data collected in the project. The GO grant will extend the follow-up of LMCI and normal subjects who were enrolled in ADNI1 and are being carried forward in GO, and will allow analysis of all of the ADNI data that was not able to be done in the initial grant (since it was a data collection grant, and few funds were provided for analysis) as well as analysis of the data from this GO project, to test hypotheses and perform data explorations.

4.3. Future directions of ADNI

Funding for ADNI1 ends October 1, 2010. The future of ADNI will depend on a successful competitive renewal (termed ADNI2). ADNI2 will be focused on predictors, outcomes, and clinical trial design, but fulfillment of these aims will add considerably to what is known about the pathophysiological sequence of changes in the brain that occur across the continuum from normal aging to MCI to AD dementia. Now the major goals of ADNI, therefore, are as folllows: (1) To identify and validate imaging and blood/CSF biomarker predictors of cognitive decline/dementia for early detection of AD; (2) To identify and validate imaging and blood/CSF biomarker outcomes that reflect progression of AD pathology; and (3) To develop information leading to improved clinical trials of treatments to slow disease progression, ultimately contributing to the prevention of AD dementia.

5. Summary

Taken together, ADNI is the only multisite longitudinal observational clinical/imaging/biomarker study being performed in the U.S. ADNI data are widely available to all scientists throughout the world without embargo through the UCLA/LONI/ADNI website. ADNI has already demonstrated its high value by providing a great deal of scientific information, and providing information for development of clinical trial protocols that are being used in several current phase 3 studies. ADNI also serves as a model of ADNI-like efforts in other countries. The continuation of this study, through the GO and, hopefully, ADNI2 grant will contribute considerably to the development of new diagnostic approaches, improved clinical trials, and to the identification of effective treatments that slow the progression of AD pathology in demented and nondemented subjects. Ultimately, the results from ADNI will contribute considerably to the development of AD treatment trials and to effective measures that prevent the development of AD.

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This article is dedicated to Leon Thal, who passed away 1 year after ADNI began. His vision was critical in the creation and successful funding of ADNI.

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Appendix: End notes

[A1]The Tables below show the schedule of events and scope of work performed for ADNI1, and the proposed work for the funded GO grant and ADNI2 which was under submission at the time of writing this manuscript. Table A1 shows the years for ADNI1, GO, and ADNI2 and how Year 1of the GO grant overlaps with Year 6 of ADNI1, and how Year 2 of the GO grant overlaps with Year 1 of ADNI2.

[A2]Table A2 shows the schedule of events for ADNI1. Year 1 was the preparatory phase with little enrolment. Year 6 just began, and thus the actual number of subjects or scans is not known.

[A3]Table A3 shows the subjects enrolled in the GO grant study, including existing subjects from ADNI1 and newly enrolled subjects.

[A4]Table A4 shows the schedule of events for the proposed ADNI2, which, if funded, would begin on September 1, 2010.

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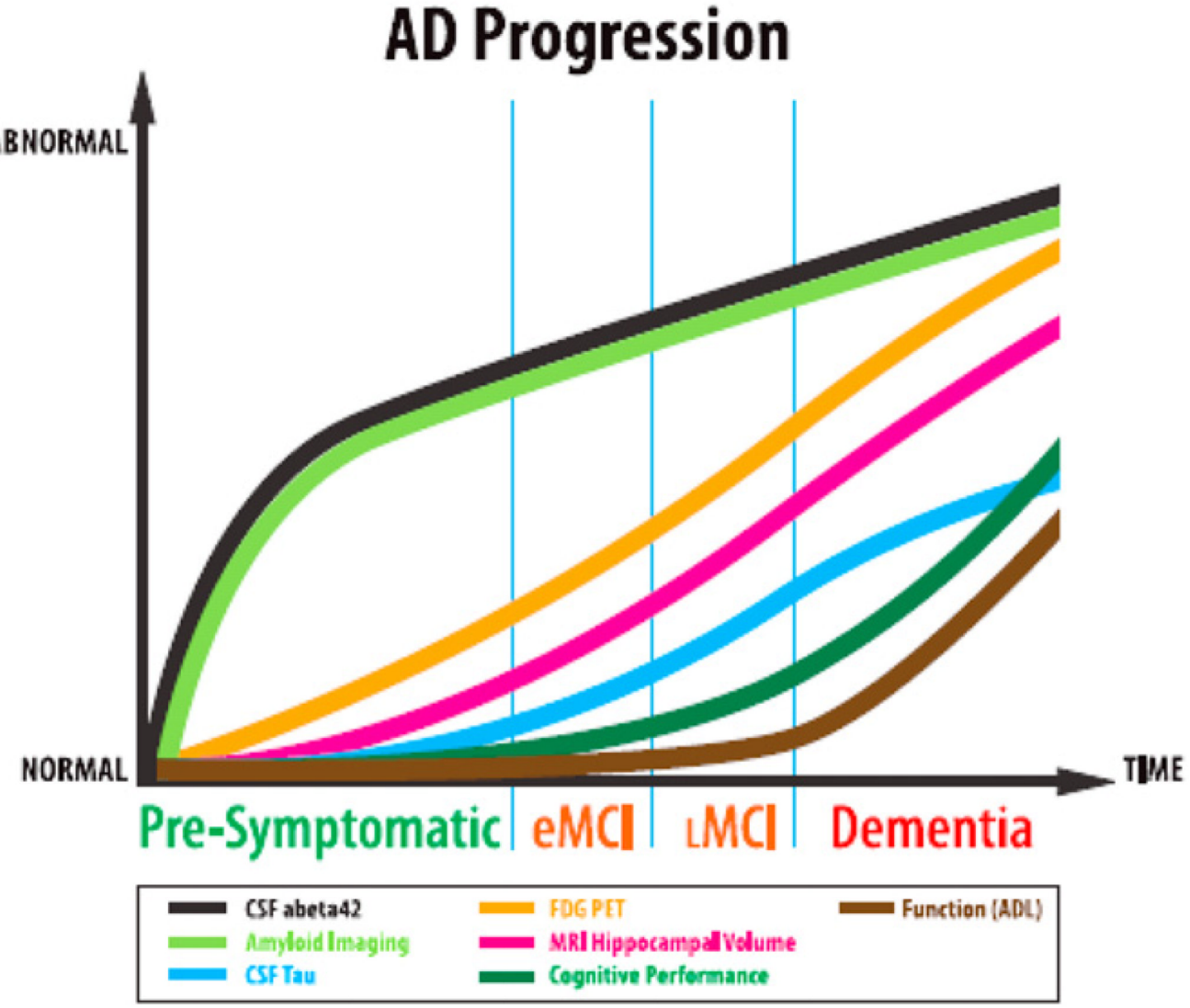

Fig. 1.
Overall model of changes in the progression from normal aging to MCI to AD.

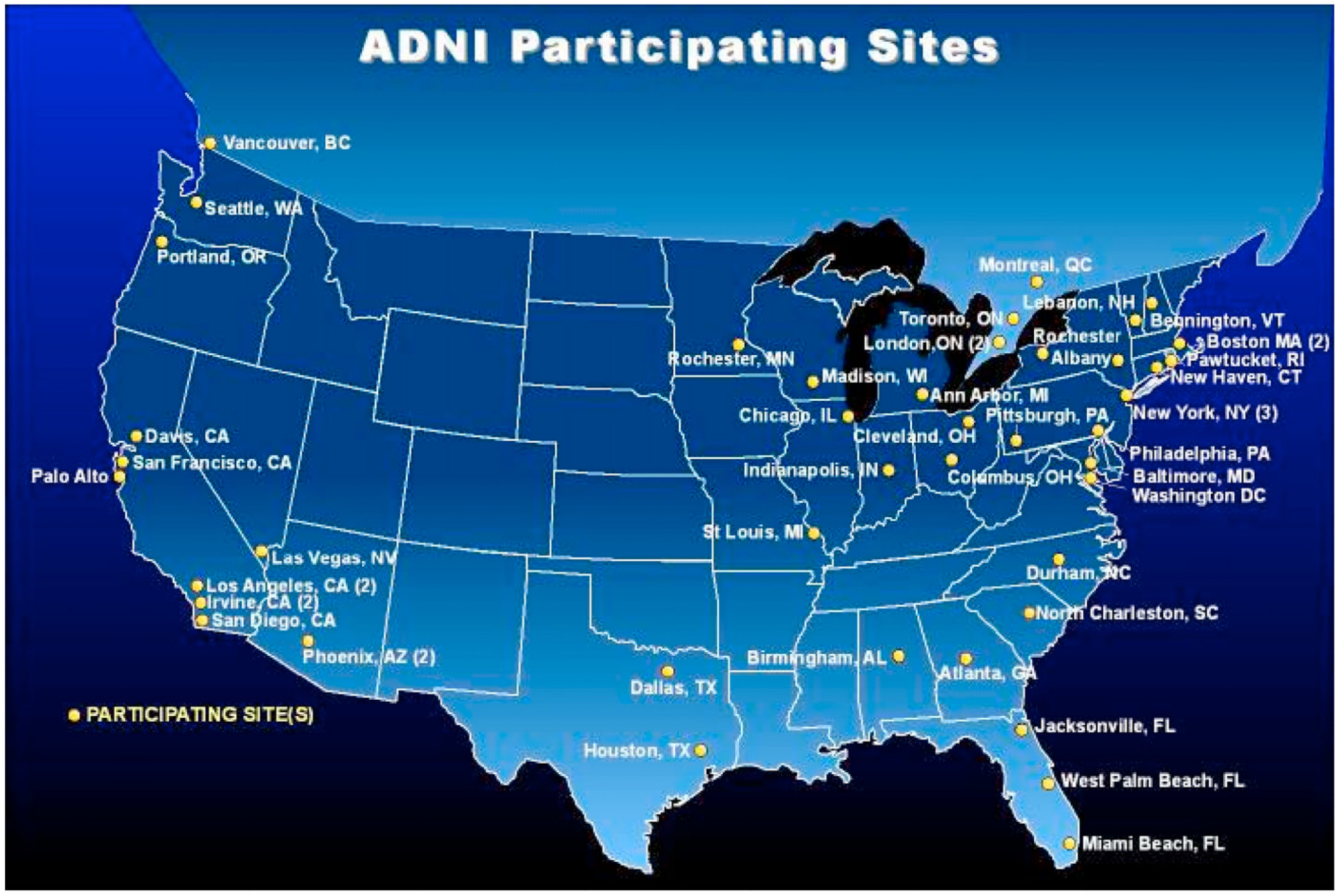

Fig. 2.
Patient recruitment sites in ADNI (provided by Sarah Walter at ADCS).

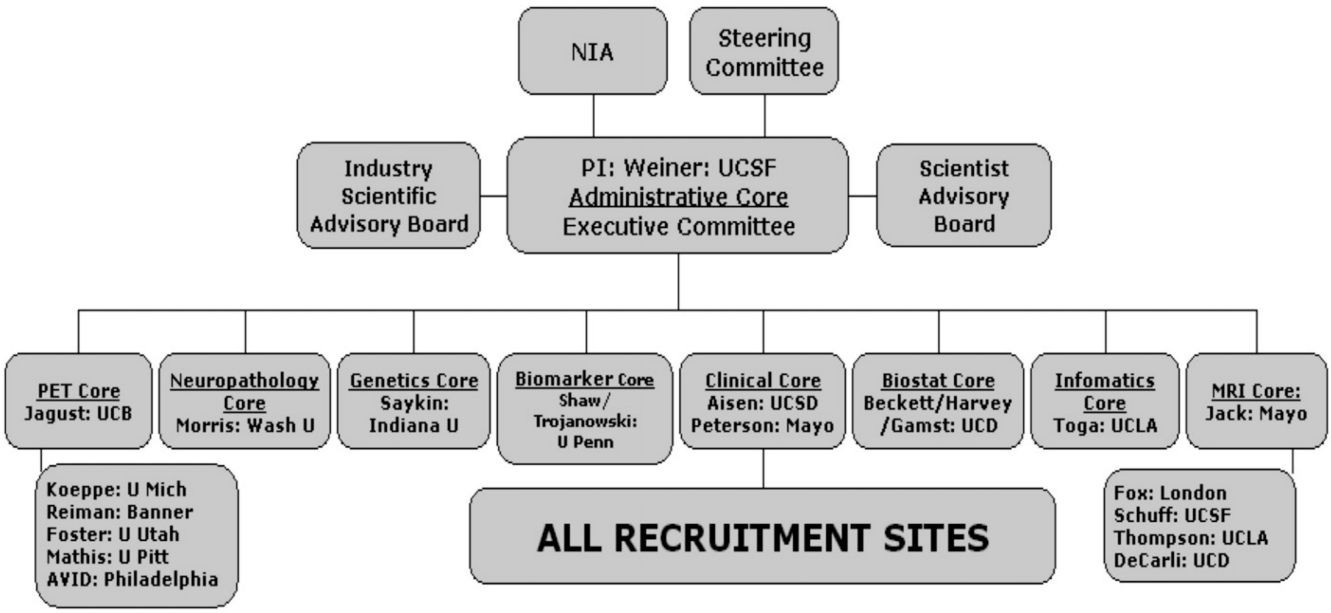

Fig. 3.
Governance and organization of ADNI.

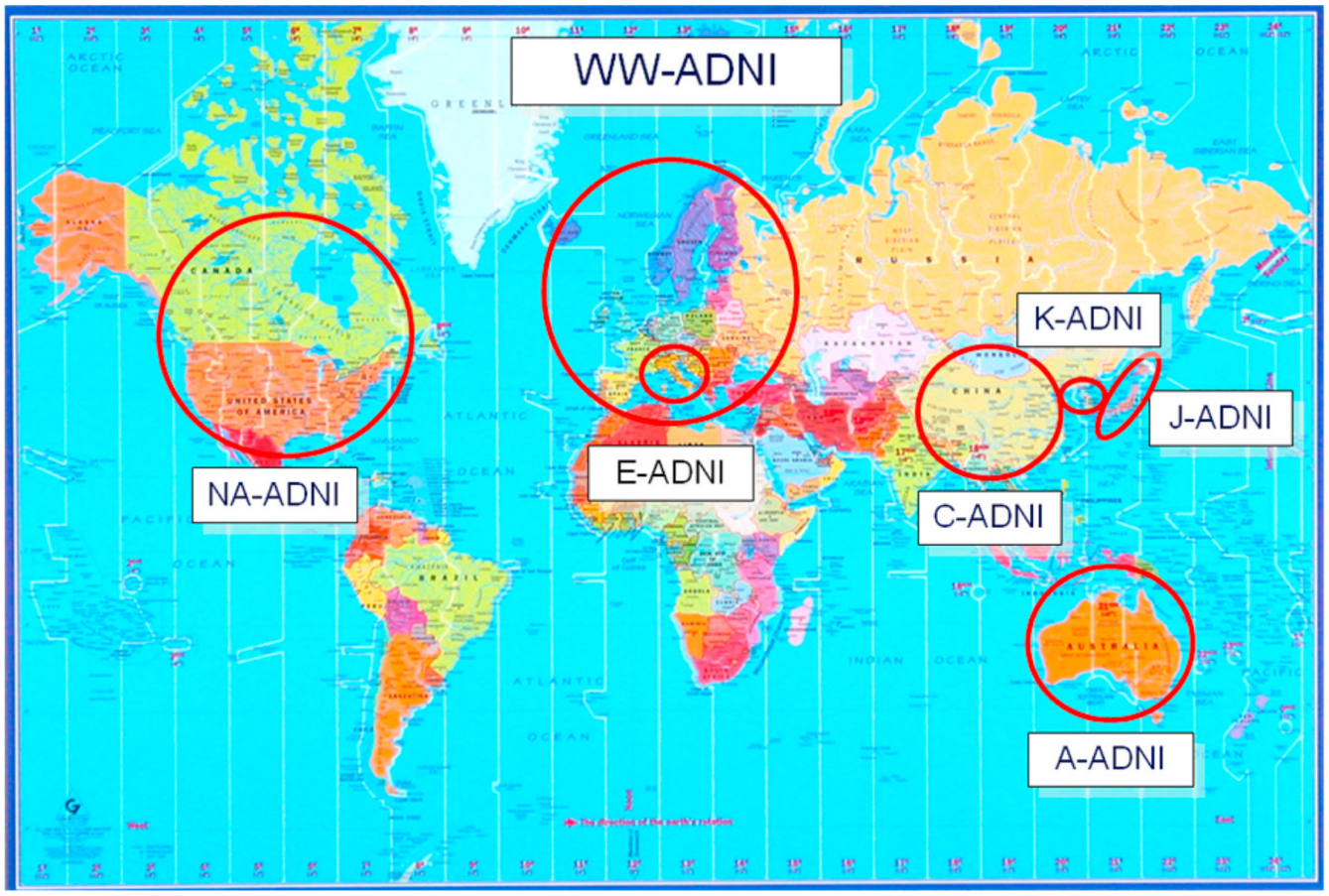

Fig. 4.
Map showing all ADNI and ADNI-like efforts in the world (Figure kindly provided by Maria Carillo of the Alzheimer's Association).

Table 1

ADNI site table

Site	City	State	Site PI	Study coordinator
Oregon Health and Science University	Portland	OR	Kaye, Jeffrey	Dolen, Sara
University of Southern California	Los Angeles	CA	Schneider, Lon	Becerra, Mauricio
University of California, San Diego	La Jolla	CA	Brewer, James	Vanderswag, Helen
University of Michigan, Ann Arbor	Ann Arbor	MI	Heidebrink, Judith	Lord, Joanne
Mayo Clinic, Rochester	Rochester	MN	Petersen, Ronald	Johnson, Kris
Baylor College of Medicine	Houston	TX	Doody, Rachelle	Chowdhury, Munir
Columbia University	New York	NY	Stern, Yaakov	Yeung, Philip
Washington University, St. Louis	St. Louis	MO	Morris, John	Oliver, Angela
University of Alabama, Birmingham	Birmingham	AL	Marson, Daniel	Ledlow, Denise
Mount Sinai School of Medicine	New York	NY	Grossman, Hillel	Marzloff, George
Rush University Medical Center	Chicago	IL	deToledo-Morrell, Leyla	Samuels, Patricia
Wien Center for Clinical Research	Miami Beach	FL	Duara, Ranjan	Roberts, Peggy
Johns Hopkins University	Baltimore	MD	Albert, Marilyn	Shao, Shuai
New York University Medical Center	New York	NY	Rusinek, Henry	Glodzik-Sobanska, Lidia
Duke University Medical Center	Durham	NC	Doraiswamy, P. Murali	Aiello, Marilyn
University of Pennsylvania	Philadelphia	PA	Arnold, Steven	Nunez-Lopez, Jessica
University of Kentucky	Lexington	KY	Smith, Charles	Martin, Barbara
University of Pittsburgh	Pittsburgh	PA	Lopez, Oscar	Oakley, MaryAnn
University of Rochester Medical Center	Rochester	NY	Ismail, M. Saleem	Brand, Connie
University of California, Irvine	Irvine	CA	Mulnard, Ruth	McAdams-Ortiz, Catherine
University of Texas, Southwestern MC	Dallas	TX	Womack, Kyle	Martin-Cook
Emory University	Atlanta	GA	Levey, Allan	Cellar, Janet
University of Kansas	Kansas City	KS	Burns, Jeffrey	Laubinger, Pat
University of California, Los Angeles	Los Angeles	CA	Apostolova, Liana	Eastman, Jennifer
Mayo Clinic, Jacksonville	Jacksonville	FL	Graff-Radford, Neill	Johnson, Heather
Indiana University	Indianapolis	IN	Farlow, Martin	Herring, Scott
Yale University School of Medicine	New Haven	CT	Van Dyck, Christopher	Benincasa, Amanda
McGill University / Jewish General Hospital Memory Clinic	Montreal	QC	Chertkow, Howard	Hosein, Chris
Sunnybrook Health Sciences Centre	Toronto	Ontario	Black, Sandra	Lawrence, Joanne
University of British Columiba, Clinic for AD & Related	Vancouver	BC	Hsiung, Robin	Mudge, Benita
St. Joseph's Health Center-Cognitive Neurology	London	ON	Finger, Elizabeth	Morlog, Darlyne
Northwestern University	Chicago	IL	Wu, John (Chuang-Kuo)	Lipowski, Kristine
Medical University of South Carolina	North Charleston	SC	Mintzer, Jacobo	Williams, Arthur
Premiere Research Institute	West Palm Beach	FL	Sadowsky, Carl	Villena, Teresa
University of California, San Francisco	San Francisco	CA	Rosen, Howard	Urbano, Marissa
Georgetown University	Washington	DC	Reynolds, Brigid	Behan, Kelly
Brigham and Women's Hospital	Boston	MA	Sperling, Reisa	Frey, Meghan
Stanford / PAIRE	Palo Alto	CA	Yesavage, Jerome	

Site	City	State	Site PI	Study coordinator
Banner Sun Health Research Institute	Sun City	AZ	Sabbagh, Marwan	Sirrel, Sherye
Boston University	Boston	MA	Killiany, Ron	Wulff, Megan
Howard University	Washington	DC	Obisesan, Thomas	Wolday, Saba
Case Western Reserve University	Beachwood	OH	Lemer, Alan	Hudson, Jr., Leon
University of California, Davis	Martinez	CA	Olichney, John	Vieira, Katharine
Neurological Care of CNY	Syracuse	NY	Kittur, Smita	Cowley, Charity
Dent Neurologic Institute	Amherst	NY	Bates, Vernice	Rainka, Michelle
Parkwood Hospital	London	Ontario	Borrie, Michael	Best, Sarah
University of Wisconsin	Madison	WI	Johnson, Sterling	Harding, Sandra
University of California, Irvine (BIC)	Irvine	CA	Potkin, Steven	Ceballos III, Edward
Banner Alzheimer's Institute	Phoenix	AZ	Fleisher, Adam	Reeder, Stephanie
Ohio State University	Columbus	OH	Scharre, Douglas	Knick, Jennifer
Albany Medical College	Albany	NY	Zimmerman, Earl	Cowan, John
Thomas Jefferson University	Philadelphia	PA	Marenberg, Marjorie	Maloney, Eileen
Olin Neuropsychiatry Research Center	Hartford	CT	Pearlson, Godfrey	Anderson, Karen
Dartmouth Medical Center	Lebanon	NH	Saykin, Andrew	Englert, Jessica
Wake Forest University Health Sciences	Winston Salem	NC	Williamson, Jeff	Gordineer, Leslie
Rhode Island Hospital	Providence	RI	Ott, Brian	Oden, Esther
Cleveland Clinic Lou Ruvo Center for Brain Health	Las Vegas	NV	Bernick, Charles	Sholar, Michelle
Butler Hospital Memory and Aging Program	Providence	RI	Salloway, Stephen	Tirpaeck, Lincoln

Table A1

Work flow for ADNI1, GO grant and ADNI2 for each year of activity

ADNI1	2004–2005 Yr 1	2005–2006 Yr 2	2006–2007 Yr 3	2007–2008 Yr 4	2008–2009 Yr 5	2009–2010 Yr 6	2010–2011	2011–2012	2012–2013	2013–2014	2014–2015
GO						Yr 1*	Yr 2				
ADNI2							Yr 1*	Yr 2	Yr 3	Yr 4	Yr 5

*Overlapping years.

Table A2

ADNI1 scope of work

	Total subjects enrolled	2005–2006 Yr 2						2006–2007 Yr 3						2007–2008 Yr 4						2008–2009 Yr 5					
		N	CL	MRI	FDG	LP	PIB	N	CL	MRI	FDG	LP	PIB	N	CL	FDG	LP	MRI	PIB	N	CL	FDG	MRI	LP	PIB
Normals	229	139	364	235	85	75	0	205	505	480	166	109	8	187	397	81	40	252	18	187	361	79	189	31	16
MCI	402	155	478	287	106	98	0	308	916	831	329	178	21	261	655	328	91	722	63	216	537	155	302	49	40
AD	188	73	220	134	45	49	0	138	422	363	151	89	8	115	288	87	36	200	17	88	99	31	68	15	8
Total	819	367	1,062	656	236	222	0	651	1,843	1,674	646	376	37	563	1,340	496	167	1,174	98	491	997	265	559	95	64

Abbreviations: N, sample; CL, clinical visit; AMY, F18 amyloid PET scan; LP, limb puncture.

NOTE. ADNI1 recruited 819 subjects divided as follows: 229 Normals, 402 MCI and 188 AD subjects. After enrollment subjects had a baseline visit that included a clinical visit, an MRI, a PET scan in about half of the subjects and an LP in about 20% of the subjects. Subjects had follow-up visits at 6, 12, 18, 24, 30, and 36 months. AD subjects, however, were only followed up for 24 months. The follow-up visits essentially included a clinical visit, an MRI, an FDG PET scan in about 50% of the subjects and an LP in 20% of the subjects.

Table A3

GO grant

	2009–2010						2010–2011					
	Yr 1						Yr 2					
	N	CL	MRI	AMY	FDG	LP	N	CL	MRI	AMY	FDG	LP
Normals												
From ADNI1	211	105	0	105	105	0	200	200	200	100	100	110
MCI												
EMCI newly enrolled	200	300	300	200	200	120	200	300	300	0	200	120
LMCI from ADNI1	319	160	0	160	160	0	306	306	306	153	153	152
Total	730	565	300	465	465	120	706	806	806	253	453	382

NOTE. The estimated number of the current ADNI1 subjects that will be followed up in the GO Grant is 211 normal and 319 LMCI subjects, a total of 530 subjects. In year 2 we anticipate small attrition, resulting on 200 normal subjects and 306 MCI subjects for a total of 506. The enrollment of new subjects will be 200 EMCI subjects all in year 1. EMCI subjects will have an MRI visit 6 months after recruitment, that will make a total of 200 limited visits, 100 in the first year and 100 in the second year. The following tests will be done for the 530 subjects currently in ADNI: MRI scans on the second year (506). All current ADNI subjects are already scanned in year 1 under ADNI protocol. F18 amyloid scans for 265 subjects in year 1 and 253 in year 2 for a total of 518. All subjects who are having F18 amyloid PET scans will also be scanned with FDG PET. In year 2, the half of the group of subjects that did not have an FDG and part of the GO, will be scanned with FDG PET. LP on 262 subjects in year 2. The following tests will be done for newly enrolled EMCI subjects in year 1 and 2 of GO: screening and baseline visit in year 1. Clinical FU visit at the 12 month time point for all subjects. Limited FU visits at the 6 month time point for all newly recruited subjects. MRI scan at baseline for all subjects and another one at the 1 year point. In addition at the 6 month period, subjects will have one additional scan, the total on the 200 EMCI will be 100 in the first year for the GO subjects recruited in the first half of the first year and 100 in year 2 for the rest of the subjects that will be recruited in the second half of the first year. FDG scans for all new subjects at baseline and in year 2. F18 amyloid scans on all new subjects at baseline. LP on 60% of subjects at baseline and at the 1 year follow-up period.

Table A4

ADNI2 schedule of activities per year and type of subject

	2010–2011						2011–2012					2012–2013						2013–2014			2014–2015			
	Yr 1						Yr 2					Yr 3						Yr 4			Yr 5			
	N	CL	MRI	AMY	FDG	LP	N	CL	MRI	AMY	FDG	N	CL	MRI	AMY	FDG	LP	N	CL	MRI	N	CL	MRI	LP
Normals																								
From ADNI1	202						190	190	190	95	95	179	179	179	90	90	107	168	168	168	158	158	158	95
Newly enrolled	150	150	450	150	150	150	141	141	141	0	0	133	133	133	133	133	133	125	125	125	118	118	118	118
MCI																								
EMCI from GO grant	200						188	188	188	188	188	177	177	177	0	0	177	166	166	166	156	156	156	156
EMCI newly enrolled	100	100	300	100	100	100	94	94	94	0	0	88	88	88	88	88	88	83	83	83	78	78	78	78
LMCI from ADNI1	274						258	258	258	129	129	243	243	243	122	122	146	228	228	228	214	214	214	128
LMCI newly enrolled	150	150	450	150	150	150	141	141	141	0	0	133	133	133	133	133	133	125	125	125	118	118	118	118
AD																								
Newly enrolled	150	150	450	150	150	150	141	141	141	0	0	133	133	133	133	133	133	0	0	0	0	0	0	0
Total	1,226	550	1,650	550	550	550	1,153	1,153	1,153	412	412	1,086	1,086	1,086	699	699	917	895	895	895	842	842	842	693

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