

The Alzheimer's Disease Neuroimaging Initiative

a report by

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In 2000, Alzheimer's disease (AD), the most common form of dementia, afflicted 4.5 million people in the US – approximately 10% of the population over 60. As the population ages over the next several decades, this number is expected to increase. Unless some treatment is found to delay or prevent its onset, over 13 million cases of AD are estimated by 2050.¹ Mild cognitive impairment (MCI), often a prodrome of AD, afflicts many more people. According to estimates used by the Alzheimer's Association and the National Institute on Aging (NIA), the cost of AD to the US economy is over US\$100 billion per year.

The AD Neuroimaging Initiative

Last fall, the NIA, a component of the National Institutes of Health (NIH), and its partners began funding the AD Neuroimaging Initiative (ADNI). NIA leads the federal effort in research on AD. The ADNI is expected to become a landmark study in the development of neuroimaging and other biomarkers for the disease.

The purpose of the five-year ADNI is to develop a multi-site, longitudinal, prospective, naturalistic study of normal cognitive aging, MCI, and AD to facilitate the scientific evaluation of neuroimaging magnetic resonance imaging (MRI) positron emission tomography (PET), and other biomarkers for the onset and progression of MCI and AD. A primary goal of the initiative is to identify the biomarkers of disease progression that are most promising for use as surrogate end-points in phase 2 and 3 clinical trials for the prevention and treatment of AD.

An essential feature of the ADNI is that the clinical, neuropsychological, imaging, and biological data and biological samples will be made available to all qualified scientific investigators as a public domain research resource.

Another aim of the initiative is to develop improved

methods that will lead to uniform standards for the multi-site collection, quality assurance (QA)/quality control, and distribution/sharing of MRI and PET data on patients with AD, MCI, and elderly controls.

At the approximate 50 clinical sites involved in the ADNI in the US and Canada, investigators will collect serial clinical, neuropsychological, biological, and imaging data on 400 people with MCI, 200 with early AD, and 200 elderly controls. All subjects will undergo 1.5T structural MRI scans; a subset will also be scanned using 3T scanners. PET scans will be obtained on another subset of participants to assess brain function by measuring the rate of glucose metabolism in various regions of the brain. Serial blood, cerebrospinal fluid (CSF), and urine samples will be collected for analyses for potential biomarkers of disease progression, including genomic, proteomic, and metabolomic markers that can be correlated with clinical, neuropsychological, and imaging data. Immortalized cell lines will also be established.

Biomarkers for AD

Advances in the understanding of the pathophysiology and genetics of AD are providing opportunities for developing disease-modifying therapies. As promising new treatments develop to slow or prevent AD, the need for biomarkers that can track the progress of the disease and identify it early becomes increasingly urgent. Biomarkers can be in the form of a test in CSF or blood, such as cholesterol levels in heart disease (HD), or can come from brain scans.² Studies have demonstrated that imaging parameters are more sensitive and consistent measures of disease progression than cognitive assessment. Some studies have shown that imaging measures correlate with cognitive test performance in MCI and AD^{3,4} – an initial step in the validation of markers that accurately predict the course of disease. A slowed rate of atrophy in a structure known to be affected by AD together with neuropsychological test data indicating that cognitive

1. Hebert L E, Scherr P A, Bienias J L, Bennet D A, Evans D A, "Alzheimer Disease in the U.S. Population", *Arch. Neurol.* (2003); 60: pp. 1,119–1,122.

2. Frank R, Hargreaves R, "Clinical Biomarkers in Drug Discovery and Development", *Nat. Rev. Drug Discov.* (2003); 2: pp. 566–580.

function was stabilizing or improving would be strong evidence for a disease-modifying effect. The technical feasibility of using structural MRI measures as a surrogate end-point of disease progression in multi-center clinical trials has been demonstrated.⁵

A number of biological substances in the blood, CSF, and urine now appear to have considerable potential for measuring progression in AD.²⁶ Some of the more promising, for example, include levels of tau, a component neurofibrillary tangles, a pathological hallmark of AD; indicators of inflammation such as C-reactive protein (CRP) and alpha-anti-chymotrypsin; and measures of oxidative stress such as oxysterols and isoprostanes.

A marker that signals whether a disease is becoming better or worse can greatly facilitate the evaluation of drugs in clinical trials, decreasing the time and cost of clinical trials. In phase 2 trials, for example, markers can help to rapidly identify appropriate doses, assess safety, and compare drugs in early development.²⁷ Markers can be useful not only for tracking the progression of disease, but for diagnosing AD early on.

The ADNI will help to delineate methods that provide maximum power in determining treatment effects in clinical trials of drugs for AD and MCI that can be used for the future design of clinical trials.

Public-Private Partnership

The ADNI is a partnership, combining the resources and expertise of the NIA, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), academic investigators, pharmaceutical companies, the US Food and Drug Administration (FDA), the NIH Foundation, the Alzheimer's Association, and the Institute for the Study of Aging. Staff from all partners have contributed advice and ideas for the development of the ADNI since its inception.

Collaborating with the FDA on projects such as the ADNI helps the NIH bridge the gap between research and the regulatory process, speeding the

fruits of research into treatments for disease, a priority for both agencies. The FDA is increasingly accepting of surrogate end-points based on imaging that are not yet fully validated, including as primary end-points in pivotal trials (recent examples include the arthritis drug etanercept, and antineoplastic agent oxaliplatin), given the marker is reasonably likely to predict clinical benefit, a condition that the ADNI can help demonstrate. Imaging end-points have contributed to drug development in at least one disease of the central nervous system (CNS) – multiple sclerosis (MS).²⁷

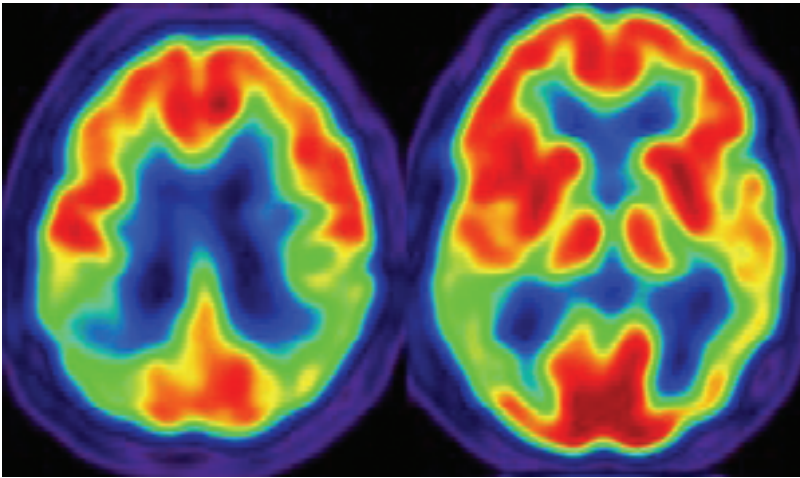
The total projected cost for the ADNI is US\$60 million over five years. At this time, industry partners have committed to contributing over one-third of these funds. Companies make their contributions to the NIH Foundation, which distributes funds to NIA as they are needed for the study. Besides managing and administering funds, NIH Foundation staff also help to recruit industry partners, organize meetings among them, and keep them up-to-date on developments in ADNI.

Ancillary studies to the ADNI are anticipated to include a variety of methods of data processing and analyses, neuroimaging studies to run in parallel with the ADNI, using techniques such as magnetic resonance spectroscopy, functional MRI, and diffusion-tensor imaging, and autopsy follow-up studies.

The grant funding for the ADNI was awarded to Dr Michael Weiner as principal investigator, at the Northern California Institute for Research and Education, a foundation affiliated with the Department of Veteran Affairs. Dr Weiner is also affiliated with the Veterans Affairs Medical Center in San Francisco and the University of California at San Francisco. The Coordinating Center for the ADNI is based at the University of California at San Diego under the direction of Leon Thal, MD. The clinical core of the study is being directed by Ronald Petersen, MD, PhD, from the Mayo Clinic. The MRI component of the neuroimaging core is being directed by Clifford Jack, MD from Mayo, and the PET component by William Jagust, MD, from the University of California, Berkeley. John Trojanowski, MD, PhD (University of

3. Jack C R, Petersen R C, Xu Y et al., "Rates of Hippocampal Atrophy Correlate with Change in Clinical Status in Aging and AD", *Neurol.* (2000); 55: pp. 484–489.
4. Grundman M, Jack C R, Petersen R C et al., *Alzheimer's Disease Cooperative Study*, "Hippocampal Volume is Associated with memory but not Nonmemory Cognitive Performance in Patients with Mild Cognitive Impairment", *J. Molec. Neurosc.* (2003);20, pp. 241–248.
5. Jack C R, Slomkowski M, Gracon S et al., "MRI as a Biomarker of Disease Progression in a Therapeutic Trial of Milameline for AD", *Neurol.* (2003);60: pp. 253–260.
6. Frank R A, Galasko D, Hampel H et al., "Biological Markers for Therapeutic Trials in Alzheimer's Disease: Proceedings of the Biological Markers Working Group; NIA Initiative on Neuroimaging in Alzheimer's Disease", *Neurobiol. Aging* (2003);24: pp. 521–536.
7. Comi G, Filippi M, "Clinical Trials in Multiple Sclerosis: Methodological Issues", *Curr. Opin. Neurol.* (2005);18: pp. 245–252.

Figure 1



Pennsylvania), is directing the laboratory biomarkers component; Arthur Toga, PhD (UCLA), is director of the informatics core; and Laurel Beckett, PhD (University of California, Davis), is director of the statistics core. The

Steering Committee for the ADNI comprises the previously mentioned scientists, the principal investigators of each clinical sites, scientists representing each of the pharmaceutical company partners, representatives from the NIH and FDA, and the NIH Foundation.

By facilitating the development of neuroimaging and biochemical markers, the ADNI and its ancillary studies should decrease the time and cost of phase 2 and 3 clinical trials, and increase the safety and efficiency of drug development for AD. The development and establishment of methods for the multi-site collection, QA/control, and distribution/sharing of neuroimaging, biological, and clinical data should also further these goals.

Finally, in its sharing of knowledge and resources among academic, industry, and government institutions, the ADNI can serve as a model for future scientific partnerships to facilitate biomarker and drug development for other diseases that affect so many lives. ■