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Impact of the Alzheimer's Disease Neuroimaging Initiative, 2004 to 2014

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Abstract

Introduction: The Alzheimer's Disease Neuroimaging Initiative (ADNI) was established in 2004 to facilitate the development of effective treatments for Alzheimer's disease (AD) by validating biomarkers for AD clinical trials.

Methods: We searched for ADNI publications using established methods.

Results: ADNI has (1) developed standardized biomarkers for use in clinical trial subject selection and as surrogate outcome measures; (2) standardized protocols for use across multiple centers; (3) initiated worldwide ADNI; (4) inspired initiatives investigating traumatic brain injury and post-traumatic stress disorder in military populations, and depression, respectively, as an AD risk factor; (5) acted as a data-sharing model; (6) generated data used in over 600 publications, leading to the identification of novel AD risk alleles, and an understanding of the relationship between biomarkers and AD progression; and (7) inspired other public-private partnerships developing biomarkers for Parkinson's disease and multiple sclerosis.

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Discussion: ADNI has made myriad impacts in its first decade. A competitive renewal of the project in 2015 would see the use of newly developed tau imaging ligands, and the continued development of recruitment strategies and outcome measures for clinical trials.

Keywords: Alzheimer's disease; Data-sharing; Amyloid phenotyping; Clinical trial biomarkers; Tau imaging; AD biomarker signature; Worldwide ADNI

1. Introduction

The overall goal of the Alzheimer's Disease Neuroimaging Initiative (ADNI), established in 2004, is to facilitate the development of effective treatments for Alzheimer's disease (AD) by validating biomarkers for AD clinical trials. Although no treatment has yet been shown to slow the progression of AD, the many accomplishments of ADNI have served as a model for other initiatives and programs.

A framework for pathophysiological changes occurring during disease progression was developed in the 1990s which centered on the accumulation of amyloid as a central pathogenic event [1]. However, at the turn of the century, details of the timing of the cascade of antecedent events leading to neurodegeneration and their relationship to clinical phenotypes were lacking [2]. The clinical diagnosis of AD was almost exclusively based on clinical assessment, the apolipoprotein E (*APOE*) ε4 allele was the primary known genetic AD risk factor, and mild cognitive impairment (MCI) had been recently recognized as a prodromal state of the disease [3,4]. The pharmaceutical industry was developing disease-modifying treatments to be tested, but clinical trials of these treatments were limited because clinical and cognitive outcome measures were the only ways to detect treatment effects. Patient functioning and cognition, especially memory, are extremely important, but brain function is affected by many factors other than AD pathology. Therefore, clinical and cognitive measurements may not be sufficiently powerful to detect the effects of treatments to slow AD progression within time and size constraints of clinical trials. Magnetic resonance imaging (MRI) and positron emission tomography (PET) biomarkers offered more precise alternatives to cognitive tests to assess disease progression, especially early in the disease. If such biomarkers were validated, the cost and length of drug trials could be reduced. Furthermore, the AD field would greatly benefit from surrogate outcome measures, that is, biomarkers of disease progression with greater statistical power than clinical or cognitive measurements used alone. Alternatively, improvement of the ability of cognitive tests to assess disease progression would also benefit clinical trials. The efficacy of these biomarkers could be accurately assessed using a standardized cohort using standardized methods [5,6] and ADNI was established primarily to fill this need.

Designed as a multisite, longitudinal study of normal cognitive aging, MCI, and early AD, the primary goal of ADNI was to develop imaging and other biomarkers for clinical trials [5,6]. To achieve this, ADNI enrolled a large cohort (>800) of participants across the spectrum of the disease [7] and developed optimized and standardized methods for use in a multisite setting to characterize the cohort with clinical, cognitive, MRI, PET, biofluid, and genetics measurements. One aim was to develop biomarkers that could consistently identify the disease with high sensitivity and specificity at an earlier stage and to better monitor disease progression and treatment effects. As the need for effective AD treatments was so pressing and the task of developing them was too great for any one public agency or private company, funding was secured from both the public and private sector, establishing ADNI as a model for public-private partnerships. Initial funding for a 5-year study came from the National Institute on Aging ($40 million), 13 pharmaceutical companies, and 2 not-for-profit foundations ($20 million). After the initial funding of ADNI-1 in 2004, further Foundation and Industry funding allowed the addition of PET amyloid imaging using the radiotracer ^{11}C-Pittsburgh Compound B, genome-wide association studies (GWAS), and additional cerebrospinal fluid (CSF) analysis [8]. A unique feature of the original ADNI grant (now called ADNI-1) was that all clinical, cognitive, imaging, and biomarker data collected by the ADNI database would be immediately available to all scientists in the world who requested it, with no embargo. ADNI-1 was then extended by a Grand Opportunities grant (ADNI-GO). In 2010, ADNI was competitively renewed (termed ADNI-2) with funding through mid-2016. Each study used ongoing advances in imaging and genetics technologies, and ADNI-GO and ADNI-2 included an additional cohort of early MCI patients to study the earlier stages of the disease. Subjects enrolled in ADNI-2 and those continuing from ADNI-1 and ADNI-GO have had amyloid PET scanning with florbetapir, lumbar puncture for CSF analysis, and fluorodeoxyglucose-PET, MRI, and an extensive clinical and cognitive battery.

ADNI is conducted at 57 academic sites across the United States and Canada and comprises eight cores (clinical, MRI, PET, biomarker, neuropathology, genetics, biostatistics, and informatics) under supervision of the Administrative Core, led by Dr Michael W. Weiner [5]. ADNI is governed by Steering Committee including representatives from all funding sources and the principal investigators of ADNI sites. The Industry Scientific Advisory Board provides input from pharmaceutical stakeholders. The structure of the study, detailed in ref. [5], has been integral to the success