## Impact of the Alzheimer’s Disease Neuroimaging Initiative, 2004-2014.

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### Abstract

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. Over the last decade, ADNI has developed standardized biomarkers for use in subject selection and as surrogate outcome measures. Standardization of ADNI protocols has enabled the direct comparison of results across multiple centers of research and has enabled the formation of Worldwide ADNI comprising 8 separate initiatives that are providing global data on disease progression in diverse ethnic groups. Two additional similar initiatives employing ADNI structure and protocols are focused on traumatic brain injury and post-traumatic stress disorder in military populations, and depression, respectively, as an AD risk factor. ADNI has acted as a model for the free sharing of data as evidenced by over 5 million downloads by over 3000 qualified scientists worldwide. ADNI data have been used in approximately 600 scientific publications which have most significantly established relationships between biomarkers, memory and *APOE*, assessed a widely accepted model for biomarker dynamics in AD pathogenesis, and developed a biomarker ‘signature‘ for AD. ADNI genetics data have been an integral part of data sets of numerous GWAS and other studies leading to identification and/or confirmation of over 20 novel AD risk alleles. Finally ADNI has inspired other public-private partnerships focused on developing biomarkers for and understanding the pathophysiology of Parkinson’s disease and Multiple Sclerosis. The second decade of ADNI will see the use of newly developed tau imaging ligands in preparation for a competitive renewal of the project in 2015.

### Introduction

The overall goal of the Alzheimer’s Disease Neuroimaging Initiative (ADNI), established in 2004 is to facilitate 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.

At the turn of the century, the AD research landscape was one which lacked a comprehensive pathophysiological model of disease progression. The clinical diagnosis of AD was almost exclusively based on clinical assessment. The *APOE* 4 allele was the primary known genetic AD risk factor and mild cognitive impairment (MCI) had been recognized as a prodromal state of the disease ([1](#_ENREF_1)) ([2](#_ENREF_2)). The pharmaceutical industry was developing disease-modifying treatments to be tested, although it was widely recognized that clinical trials of these treatments were limited because clinical and cognitive outcome measures were the only ways to detect treatment effects. Although patient functioning and cognition, especially memory, are extremely important, it is generally accepted that brain function is affected by many factors other than the progression of AD pathology. Therefore, the statistical power of clinical and cognitive measurements to detect the effects of treatments aimed at slowing progression of AD is poor, leading to long trials with large sample sizes. Interest burgeoned in MRI and PET biomarkers as more precise alternatives to cognitive tests for the assessment of disease progression, especially at earlier stages of the disease. If such biomarkers could be developed and validated, the cost and length of drug trials could be reduced. Furthermore, the AD field would greatly benefit from surrogate outcome measures, i.e. biomarkers that accurately detect disease progression with higher statistical power than clinical or cognitive measurements. However, it was soon recognized that the efficacy of these biomarkers could only be accurately assessed using a standardized cohort using standardized methods ([3](#_ENREF_3), [4](#_ENREF_4)). ADNI was established primarily to fill this need.

Designed as a multisite, longitudinal, prospective, naturalistic study of normal cognitive aging, MCI and early AD, the primary goal of ADNI was to develop imaging and other biomarkers for use in clinical trials ([3](#_ENREF_3), [4](#_ENREF_4)). To achieve this, ADNI enrolled a large cohort (>800) of participants across the spectrum of the disease and developed optimized and standardized methods that could be used in a multi-site setting to characterize the cohort using clinical, cognitive, MRI, PET, biofluid and genetics measurements. One aim was to identify those biomarkers able to identify the disease with high sensitivity and specificity at an earlier stage and to better monitor disease progression and thus treatment effects. Recognizing that the need for effective AD treatments was so pressing and the task of developing 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), and 13 pharmaceutical companies and 2 not-for-profit foundations ($20 million).

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. Although there were concerns that this unprecedented data sharing would lead to problems, it is now generally acknowledged that this open access has been very successful. ADNI data has been used in numerous publications, meta-analyses and a recent crowd-sourcing challenge. The database is serving as a model for a number of other initiatives.

ADNI is conducted over 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. 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. A detailed description of the study structure is given in ([3](#_ENREF_3)).

After the initial funding of ADNI-1 in 2004, further foundation and industry funding allowed the addition of PET amyloid imaging using the radiotracer 11C-PiB, genome-wide association studies (GWAS) and additional cerebrospinal fluid analysis ([5](#_ENREF_5)). 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 progressively utilized advances in imaging and genetics technologies, and ADNI-GO and ADNI-2 included an additional cohort of early MCI patients to study the disease in its nascency ([5](#_ENREF_5)). 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, as well as FDG PET, MRI, and an extensive clinical and cognitive battery.

What impacts has ADNI made over the last decade? The pharmaceutical industry has benefitted from the development of standardized biomarkers and the generation of data to guide trial design. Investigators worldwide have benefitted from access to ADNI data and samples, resulting in progress often far beyond the original ADNI mandate. ADNI genetics data is now being employed in a whole genome sequencing project in a ‘big data’ approach to finding AD treatments. Our understanding of AD pathophysiology and genetics has benefitted from many of the approximately 600 publications using ADNI data. In particular, the AD model reported by Jack et al ([6](#_ENREF_6)) has provided the field an overall conceptual model which has stimulated hypothesis testing and other studies. Amyloid phenotyping using amyloid PET scans and CSF measurements has become an established method for the identification of AD pathology in observational studies and treatment trials. The research community has benefitted from the development of a plethora of methodologies using ADNI data, often applicable to areas outside AD research. ADNI structure and methodologies are now also being employed in investigations into the role of depression in AD and of special risk factors for AD in veterans. In addition, the ADNI model has fostered similar projects worldwide and inspired initiatives in other diseases such as Parkinson’s disease and Multiple Sclerosis.

One measure of the national and international impact of ADNI was its identification by the US government in 2011 as a key player in achieving goals of accelerating the development of treatments that would prevent, halt, or reverse the course of AD and improving early diagnosis in the National Plan to Address Alzheimer’s Disease(U.S. Department of Health and Human Services)developed in response to the National Alzheimer’s Project Act. This paper aims to detail the achievements and impacts of ADNI from 2004 to 2014.

### Impacts of ADNI

ADNI has impacted clinical trials for AD modifying and preventative treatments

ADNI has impacted clinical trials by providing data to guide trial design and by developing standardized biomarkers and methodologies. ADNI has provided an ever richer data set and important venue for precompetitive public-private interaction around biomarkers and clinical trial methodologies for AD. CSF and hippocampal volume biomarkers remain the focus of ongoing qualification efforts with the FDA. Amyloid biomarkers are actively used for subject selection in clinical trials of candidate therapeutics. Amyloid biomarker sub-studies in the recent solanezumab and bapineuzumab Phase III programs revealed that even in AD dementia populations, more than 20% of enrolled mild and moderate AD subjects were amyloid negative by CSF Aβ or amyloid PET. Subsequent trials of anti-amyloid therapeutic candidates are requiring amyloid biomarkers at screening and amyloid positivity as an inclusion criterion. Longitudinal measures of amyloid are also being increasingly used later in the drug development process in order to assess potential disease modifying effects.

Hippocampal volume, as measured from structural MRI scans, decreases rapidly in the MCI phase preceding transition to AD dementia and is strongly associated with imminent clinical decline. While not pathologically specific, screening for reduced baseline hippocampal volume selects a more homogeneous population of rapidly declining subjects, decreasing variability in longitudinal clinical outcome measures. Hippocampal volume was also recently qualified by the European Medicines Agency for enrichment of amnestic MCI clinical trial populations, based in part on de novo analyses of ADNI data and coordinated in a precompetitive fashion by the Coalition Against Major Diseases ([7](#_ENREF_7)).

ADNI investigators have proposed new trial designs for intervention at the prodromal ([8](#_ENREF_8)) and preclinical ([9](#_ENREF_9)) stages of disease that have been adopted by academic and industry investigators, and have contributed to the development of new regulatory guidance ([10](#_ENREF_10)). In particular, the A4 trial ([11](#_ENREF_11)) launched in 2014 as an industry-academia collaboration, represents the first therapeutic trial in preclinical sporadic AD. A second major study utilizing a similar design will be launched in 2015.

At the outset of ADNI, a major obstacle to producing meaningful data for analysis was the development of standardized methodologies. A major collaborative effort has resulted in a set of protocols (available at <http://adni.loni.usc.edu/methods/>) that allow the direct comparison of results worldwide ([3](#_ENREF_3)). As a result of ADNI’s contributions, pharmaceutical companies developing disease-modifying treatments for AD, and studies funded by the NIH and private foundations have employed ADNI methodologies in virtually all their clinical trials.

Positron emission tomography

Acquisition methods, quality control standards and methods for preparing data for FDG PET, and amyloid imaging using Pittsburgh's compound and Florbetapir were developed by the ADNI PET core ([12](#_ENREF_12)). The standardized protocols were designed to be compatible with multiple commercially available scanner hardware and software combinations which could result in a twofold difference in intrinsic resolution. Raw PET images from all sites undergo quality control processes at the ADNI PET site at the University of Michigan. The gold standard digital Hoffman Phantom is used as a comparison to correct image resolution, and to enhance image uniformity, producing a variety of sets of images such as images that are registered to one another or oriented to a standardized grid. Different ADNI sites are then responsible for a variety of image analysis processes such as SPM5 to examine correlations between changes in glucose metabolism and cognition and to map cross-sectional differences between patient groups, and the determination of SUVR in multiple regions of interest. These protocols are detailed at <http://adni.loni.usc.edu/methods/pet-analysis/> and result in a set of images available at LONI that are in the form that can be readily analyzed by investigators. The development of the standardized methodologies has clearly demonstrated that multicenter PET amyloid imaging is both feasible and capable of producing data sets of great value to investigators.

Magnetic resonance imaging

The development of standardized MRI procedures by the ADNI MRI core for use in the multiple ADNI centers represents a major contribution of the initiative to the scientific community. Protocols needed to be compatible with three different vendors of scanners (GE, Siemens, and Philips), a variety of hardware/software configurations within each vendor product line, and two MRI field strengths. Methods were initially developed using technology widely available at the beginning of ADNI with the philosophy that the protocol must maximize scientific utility while minimizing the scan time burden placed on participants ([13](#_ENREF_13)). Pulse sequences were optimized for longitudinal scans to ensure stability and reproducibility ([14](#_ENREF_14)). The final protocol could be run in less than 30 min, captured both structural information and detect relevant brain pathologies, and used a phantom to monitor scanner performance. The protocol also included quality control for all images acquired and post-acquisition corrections to correct scaling changes and image artifacts such as intensity non-uniformity, and warping because of gradient non-linearity ([15-17](#_ENREF_15)). A total of 38 different vendor and platform specific protocols were required to run ADNI MRI sequences at 59 sites with 89 MRI scanners. The final protocol was able to achieve consistent acquisitions across this broad distribution of sites and technologies ([15](#_ENREF_15)). Following the development of the initial protocols, it became apparent that MRI scans in ADNI also needed to image white-matter disease and so a FLAIR sequence to detect cerebrovascular disease was added to the core sequence for ADNI-GO and ADNI-2. In addition three emerging MRI applications – functional MRI, Arterial Spin Labeling Perfusion Imaging (ASL) and Diffusion Tensor Imaging (DTI) – were added in ADNI-GO and ADNI-2 as avendor specific protocols to pilot their potential use in multicenter clinical trials ([15](#_ENREF_15)). A comparison of sequences used in ADNI-1, ADNI-GO and ADNI-2 can be found at: <http://adni.loni.usc.edu/methods/mri-analysis/mri-acquisition/>.

A key factor in the success of ADNI MRI protocols has been the use of a high-resolution geometric phantom to assess the reliability of scanner hardware over longitudinal scans. Consisting of polycarbonate spheres filled with water and copper sulphate in a precise geometrical pattern, the ADNI phantom (Figure 1) is scanned after each patient to detect linear and nonlinear spatial distortion, signal-to-noise ratio, and image contrast, allowing these artifactual problems to be identified and subsequently corrected. The ADNI phantom has been shown to help correct scanner scaling errors or miscalibrations ([18](#_ENREF_18)) and to reduce between scanner imaging artifacts in longitudinal studies ([19](#_ENREF_19)). Without the monitoring of scanner performance using the ADNI phantom, it is estimated that around 20% of all scans would have been affected by these types of errors ([18](#_ENREF_18)). This phantom has been so successful that it has been used in numerous phase 2 and phase 3 treatment trials ([3](#_ENREF_3)).

With the increasing number of studies published using ADNI data came the realization that the direct comparison of results has been hampered by the lack of standardized data sets. To address this concern, the MRI core has developed a series of standardized data sets that have met rigorous quality control standards ([20](#_ENREF_20)). While it is too early to assess the impact of the standardized data sets on the analysis of MRI data, it is expected that this strategy will facilitate the direct and meaningful comparison and replication of different algorithms and promote consistency in data analysis.

Beyond the standardization of methods and data sets, MRI studies carried out with the ADNI cohort have impacted clinical trials of the number of ways. Fox and co-workers developed improved methods for measuring the rate of atrophy across multiple sites and for reducing required sample sizes ([21-23](#_ENREF_21)), and also developed automated methods for measuring brain and hippocampal volume and rates of atrophy ([21](#_ENREF_21), [24](#_ENREF_24), [25](#_ENREF_25)). These have been incorporated into large commercial clinical trials and submitted to the European Medicines Agency leading to guidance on hippocampal volume measurement in trials ([7](#_ENREF_7)).

One challenge in the selection of clinical trial populations is the heterogeneity of individual responses to treatment due to differing underlying pathologies such as vascular brain injury. The finding that the effects of white matter hyperintensities on cognition, brain atrophy and cerebral metabolism are dissociable from the effects of amyloid ([26-28](#_ENREF_26)) and likely contribute to the heterogeneity of individual responses to treatment ([29](#_ENREF_29), [30](#_ENREF_30)) support the notion that clinical trials may benefit from reducing heterogeneity through exclusion or stratification of individuals with vascular brain injury as measured by MRI.

CSF biomarkers

The ADNI Biomarker Core has developed and improved methodologies for the analysis of CSF biomarkers, initially establishing a flow-cytometry based assay using xMAP technology ([31](#_ENREF_31), [32](#_ENREF_32)) and assessing its within-site and inter-site reliability. They determined that best performance was assured by strict attention to standard operating procedures and the inclusion of appropriate quality control specimens ([33](#_ENREF_33)). Their establishment of the predictive ability of the CSF biomarker signature provided support for the lumbar puncture procedure and hastened its acceptance as a valid tool in the AD diagnosis arsenal. More recently, this Core has developed an alternative assay for the measurement of CSF A42 using two-dimensional UPLC-MS-MS, characterized the diagnostic ability of this assay using receiver-operator curves and correlation analyses and developed a surrogate matrix for calibration purposes ([34](#_ENREF_34)). The inclusion of CSF biomarkers in the newly revised NIA-AA criteria for the diagnosis of AD in research settings ([35](#_ENREF_35), [36](#_ENREF_36)) has led to the use of these assays in the selection of AD patients at the predementia stage to improve the statistical power of clinical trial design. Ongoing standardization efforts by the Biomarker Core are aimed at minimizing sources of analytical variability and developing reference methods and standardized reference materials. Assessment of the NIA-AA criteria in the ADNI cohort provided support for their utility and also highlighted possible weaknesses in their classification scheme such as the categorization of patients as ‘undefined’ or ‘uninformative’. The Biomarker Core has suggested improvements to these criteria to operationalize them in a way that would ensure the optimal stratification of patients across the AD spectrum ([37](#_ENREF_37)).

ADNI has been a model for data sharing without embargo

When ADNI was established in 2004, the concept that data generated by the initiative would be shared openly and without embargo to all qualified researchers worldwide was a relatively new and radical one. Research data was generally considered to be owned by investigators who guarded it to avoid competition, the possibility of their results of not being duplicated, or from misuse by unqualified persons. The sharing of all data associated with an experiment does allow external duplication of findings as well as meta-analyses by combining data from multiple experiments, and new experiments to be performed using the same data ([38](#_ENREF_38)). The quantity of imaging, clinical, cognitive, biochemical, and genetic data generated throughout ADNI by geographically distributed investigators has required powerful informatics systems and mechanisms of processing, integrating, and disseminating these data. With these goals in mind, the Bioinformatics Core of ADNI, led by Dr Arthur Toga, developed a sophisticated informatics infrastructure based at to the Laboratory of Neuroimaging (LONI) currently at the University of Southern California. This well-curated scientific data repository, owned collectively by ADNI rather than any participating entity, facilitates data integration, access, and sharing of data in a standardized manner with individuals with research credentials ([39](#_ENREF_39)). Also included in LONI are data generated by the Australian Imaging Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing, and from new analyses by researchers accessing data.

ADNI is recognized by the medical research community as a leading example of how timely and expensive sharing of well-characterized data can promote further research, improve drug development and therefore benefit public health ([38](#_ENREF_38)). As of 15 July 2014, there has been over 5.6 million downloads of image data, 322,940 downloads of clinical data, and 5,867 downloads of genetic data by 3234 separate downloaders (personal communication, Dr Arthur Toga).

The ADNI database has also served as model for other projects such as the Parkinson's Progression Markers Initiative (PPMI) and, very recently, the North American Registry for Care and Research in Multiple Sclerosis (NARCRMS). PPMI aims to identify biomarkers for Parkinson's Disease progression ([40](#_ENREF_40)) and shares the LONI informatics data repository. NARCRMS, a database to collect MRI and other biomarker information data from patients with MS in the United States, is modelled specifically on ADNI’s database and will provide freely available data on MS patients to clinicians, patients and pharmaceutical companies ([41](#_ENREF_41)).

ADNI shared data has also been used in studies beyond the original project mandate, playing a critical role in identifying novel AD genetic risk factors, and contributing to research sometimes completely unrelated to AD for which data from a well-characterized cohort is desirable. These include investigations into stroke, hypertension, depression, and even mapping skull shape gradients in historical population movements ([42](#_ENREF_42)).

In the mid-2013, whole genome sequencing data for the entire ADNI cohort was added to the LONI database. Funded by the Alzheimer's Association and the Brin Wojcicki Foundation, this project added around 165 terabytes of data to the repository and signalled the entry of ADNI into the world of big data. The full impact of this project has yet to be realized, but the combination of whole genome sequences with existing longitudinal assessments of neuropsychological, imaging and biological measures has the potential to allow investigators worldwide to discover new associations between rare genetic variants and these disease features and to develop novel targets for new disease modifying or preventative therapies (http://alzforum.org/news/research-news/adni-full-genetic-sequences-now-available-download).

The sum of the ADNI data repository is now being leveraged in a computational challenge jointly run by the Global CEO Initiative for Alzheimer’s Disease, DREAM and Sage Bionetworks. The Alzheimer’s Disease Big Data DREAM Challenge #1 (<https://www.synapse.org/#!Synapse:syn2290704>) challenges bioinformatics experts worldwide to predict the best biomarkers for early AD-related cognitive decline and for discordance between high amyloid levels and cognitive decline. Over 200 teams in both the public and private sector have accepted the challenge, which will also use date provided by Rush University Medical Center, and The AddNeuroMed Study. The best-performing predictive models will be tested in a similar independent data set, with results expected in early 2015. In a sense, this challenge represents the ultimate in data-sharing in which ‘crowd-sourcing’ of data analysis in a competitive manner is expected to greatly accelerate research in this area for the public good.

ADNI data have been used in over 550 citations

One measure of the impact of ADNI is the approximately 575 of scientific publications (as of July 2014) which have utilized data generated by the initiative. Around a third of these are papers describing methods ranging from the standardization of methods for use in the multi-center setting, to improvements in neuroimaging techniques, to new approaches to classifying patients and predicting their likelihood of future decline, to methods to improve genetic and statistical analyses. Around a quarter of papers describe disease progression and associations between ADNI; many papers have characterized relationships between imaging, genetic and CSF biomarkers and cognitive measures. Approximately 15% of papers have primarily focused on the improvement of clinical trial efficiency through the selection of populations more likely to progress within the time frame of a trial and by the development of more sensitive outcome measures, both imaging and clinical. The ADNI dataset has been used in another 15% of publications which have identified around 20 AD genetic risk factors beyond the *APOE* 4 allele. A smaller number focus on cognitively normal participants, world-wide ADNI (WW-ADNI) and finally the total includes a number of reviews and perspectives.

ADNI has significantly advanced our understanding of AD pathophysiology and genetics, and aided methodological development

Ultimately, the most significant contributions of ADNI data to the scientific community can be distilled to a select group of high impact publications. We have chosen the following publications based on the impact rating of the journal, number of citations, and our assessment of novelty of the concept and the influence of the work on AD research.

Establishing relationships between biomarkers, memory, and APOE genotype.

Two early landmark papers examined the relationships between CSF biomarkers, hippocampal atrophy and memory, and the effect of the *APOE* 4 allele on these measures. In cognitively normal healthy elderly subjects, Mormino et al ([43](#_ENREF_43)) found an inverse relationship between Aβ deposition (as measured by 11C-PiB uptake) and hippocampal volume and that episodic memory loss was predicted by hippocampal volume, but not by 11C-PiB uptake. This study suggested that the accumulation of amyloid may reflect the early stages of AD pathogenesis and may subsequently mediate declines in episodic memory and therefore dementia through an effect on hippocampal volume. Likewise, hippocampal atrophy was associated with increased deposition of Aβ in MCI patients in the study by Schuff et al ([44](#_ENREF_44)) who also reported that the *APOE* 4 allele exacerbated hippocampal loss in AD patients. Together, these studies have been cited more than 500 times and provided evidence that lead to the development of a model for how these crucial biomarkers changed over the process of AD pathogenesis ([45](#_ENREF_45)).

A model for biomarker dynamics in AD pathogenesis

Perhaps the most influential of ADNI papers was the work of Jack et al ([6](#_ENREF_6)) who presented a hypothetical model for biomarker dynamics in AD pathogenesis. The basic tenet of the model was that biomarkers become abnormal in a temporal order, beginning with markers of brain amyloid deposition (CSF A and amyloid PET), progressing to markers of neuronal damage (CSF-tau and FDG-PET) and ending with structural MRI which detects atrophy in certain areas typical of AD (Figure 2). The model proposed that biomarkers become abnormal in a staged but overlapping manner and each follows a sigmoidal shape over time. Critical aspects of the model were based on previous work by the same group. After investigating the relationship between rates of amyloid deposition and ventricular expansion in the ADNI cohort by examining serial 11C-PiB PET and MRI scans ([46](#_ENREF_46)) and examining relationships between the risk of progression from MCI to AD, and hippocampal atrophy and amyloid load ([47](#_ENREF_47)), Jack et al concluded that deposition of A is decoupled from cognitive decline, whereas neurodegeneration is closely associated with clinical symptoms of the disease. The deposition of A into plaques was proposed to be necessary but not sufficient for clinical manifestation of the disease. Finally, the model suggested that the time frame of disease progression differed between individuals, and that differences in individual cognitive reserve and co-morbid non-Alzhemer’s pathologies, in particular, could alter the lag between the appearance of abnormal biomarkers and cognitive decline.

The fundamental principles of this model have largely stood the test of time and accumulated evidence. The temporal ordering of biomarkers is now well-established and supported by numerous studies. Studies focused on presymptomatic patients demonstrated that pathological changes occur in the order proposed by this model, for example presymptomatic cerebral amyloid is associated with increased neurodegeneration and may be a harbinger of cognitive decline ([27](#_ENREF_27), [48](#_ENREF_48), [49](#_ENREF_49)). Other studies have supported the acceleration of neurodegeneration from control to MCI to AD patients ([50](#_ENREF_50), [51](#_ENREF_51)). There is strong evidence for the sigmoidal trajectory of amyloid biomarkers and some evidence that neurodegenerative biomarkers also follow the same pattern as they rise to abnormal levels, although the steepness of the curve appears to vary between biomarkers ([45](#_ENREF_45)). An updated model by Jack et al ([45](#_ENREF_45)) retained the essential elements of the original, primarily adjusting only the horizontal axis from disease stage to years, recognizing the influence of cognitive reserve and other factors on the clinical stage of the disease whilst acknowledging that the time scale of this axis will vary in every individual. The original model has been cited more than 1200 times and has formed the basis for numerous studies that have substantially deepened our knowledge of AD pathophysiology. The revised model may well prove to have an equal or greater impact.

A CSF biomarker signature for AD

As AD biomarkers were being developed, it was suspected that patients could be cognitively normal but biomarker-positive, thereby harboring an increased risk for the development of the disease. The question of the level at which CSF biomarkers could be considered abnormal – the cut-point defining this change in risk – was therefore a pressing one. Shaw et al ([52](#_ENREF_52)) defined specific cut points for a CSF signature for AD based on an ADNI-independent cohort of autopsy-confirmed AD and cognitively normal patients. This AD signature, which combined low Aβ42and high t-tau or p-tau181 concentrations, was then applied to the ADNI cohort. De Meyer et al ([53](#_ENREF_53)) focused their study of CSF biomarkers on cognitively normal elderly and formulated a CSF biomarker signature almost identical to that of Shaw et al – for example, their42 cut-off was 188pg/ml compared to 192 pg/ml in the former. Unexpectedly, they found that a third of patients possessed the signature which suggested that AD pathology develops at a much earlier stage than had been previously envisioned (Figure 3). This discovery would lead eventually to the finding that abnormal changes in some markers can be detected up to 10 years in advance of clinical symptoms and is in accordance with the more recent view of AD being a continuum of disease ending in dementia ([54](#_ENREF_54), [55](#_ENREF_55)). The AD CSF biomarker signature has proved remarkably accurate in diagnosing AD, reaching a sensitivity of 90-95% and a specificity of around 90% ([56](#_ENREF_56)). Diagnostic accuracy has been further enhanced by the addition of other neuroimaging and clinical measures ([42](#_ENREF_42)). These cut point values have become widely accepted as the research standard with these two papers garnering over 900 citations.

Diagnosis and prediction of future decline

Although diagnostic classification and the prediction of future decline were not original goals of ADNI, the initiative has generated a rich data set with which to explore new approaches to these challenges. Initially, cross-sectional information was targeted for both classification and prediction and more recently, longitudinal data have been used in the prediction of factors indicating clinical decline. In 2009, twin papers by the Vemuri et al first reported the use of combinations of MRI and CSF biomarkers for AD diagnosis ([57](#_ENREF_57)) and the prediction of future clinical change ([58](#_ENREF_58)) in the ADNI dataset. The first paper reported that while CSF biomarkers were not correlated with cognitive measures in any patient group, they acted to increase the diagnostic accuracy of MRI biomarkers. Likewise in the second paper, CSF biomarkers augmented the ability of MRI biomarkers to predict subsequent cognitive decline. Currently cited by over 400 papers, these studies formed the basis for many subsequent diagnosis and prediction papers and ultimately lead to far more refined methods for the selection of clinical trial populations that were likely to show measurable clinical decline within the length of the trial.

As methods were developed for the automatic classification of AD patients using anatomical MR data, the need arose for a standardized side-by-side comparison of different pre-processing strategies on classification accuracy. Cuingnet et al ([59](#_ENREF_59)) compared to 5 voxel – based approaches, three cortical approaches, and two methods based on hippocampal shape and volume using ADNI data. This thorough study allowed researchers to directly compare these methodologies which had been originally published using different data sets and parameters, and consequently became an essential reference for the development of automatic classification strategies.

The selection of AD-like features from imaging data enabled multivariate classification by reducing the "curse of dimensionality". Likewise, the selection of features that are most AD-like across multiple modalities was critical step in constructing an accurate classifier. Chen et al ([60](#_ENREF_60)) developed a  FDG-PET based hypometabolic convergence index (HCI) which was associated with the hazard for conversion to probable AD, and which in combination with hippocampal volume measurement selected MCI patients with an even higher likelihood of conversion. Zhang et al ([61](#_ENREF_61)) intrinsically selected imaging (MRI and FDG-PET) regions of interest using a linear support vector machine and combined them with levels of CSF biomarkers according to the predefined cut points. This multimodal classifier was highly accurate and marked the beginning of a proliferation of ever more efficient methods that utilized the full breadth of ADNI data for AD diagnosis and for the prediction of future decline. For instance, one paper that quickly followed ([62](#_ENREF_62)) combined a multitask feature selection with a multimodal support vector machine to integrate disparate imaging and biological data for the estimation of continuous variables such as scores neuropsychological tests.

Genetics

After a decade, ADNI has made contributions to AD genetics far beyond the original mandate of the initiative*.* Since the first ADNI genome-wide association study in 2009 ([63](#_ENREF_63)), over 200 publications using ADNI data alone or in combination with other cohorts have been reported. The ADNI Genetics core has been instrumental in pioneering GWAS which leverage the rich array of quantitative phenotypes from multiple imaging and biomarker modalities available in the ADNI data set. Significantly, these have most recently moved toward longitudinal frameworks. ADNI data have also played a vital role as subsets of the very large data sets required to gain sufficient statistical power to identify novel risk variants in these meta-analytic case-control GWAS. Together, these uses of ADNI genetics data are leading to a deeper understanding of the biological pathways involved in disease trajectory and cognitive decline. Selected highlights of ADNI GWAS and related studies in MCI and AD patients are presented below.

In 2009, the publication of the first GWAS of MRI hippocampal volume in AD ([63](#_ENREF_63)) represented the first of many ‘firsts’ for the ADNI Genetics Core. In the following two years, ADNI reported the first GWAS of CSF amyloid and tau markers ([64](#_ENREF_64)), the first whole brain ROI-based ([65](#_ENREF_65)) and voxel-based GWAS ([66](#_ENREF_66)), the first GWAS of longitudinal hippocampal MRI change ([67](#_ENREF_67))and one of the first studies of mitochondrial DNA variations in AD ([68](#_ENREF_68)). In 2012, ADNI studies were among the first to report copy number variation in AD or MCI patients ([69](#_ENREF_69)), and gene pathway analyses of memory impairment in older adults ([70](#_ENREF_70)). In 2013, the first MRI study of the recently discovered *TREM2* variant ([71](#_ENREF_71)) reported that carriers of variants in the *TREM2* gene showed faster atrophy than non-carriers, and the first GWAS of the healthy human structural connectome implicated the *SPON1* gene ([72](#_ENREF_72)). ADNI investigators also reported the first whole-exome sequencing study in MCI that identified functional variants for rate of change in hippocampal volume in MCI ([73](#_ENREF_73)), and investigated the role of *APOE* genotype in early mild cognitive impairment (E-MCI) ([74](#_ENREF_74)).

ADNI genetics data continue to enhance the biological understanding of underlying disease mechanism in studies. Kim et al ([75](#_ENREF_75)) examined influence of genetic variation on plasma protein levels in older adults using a multi-analyte panel, and confirmed previously identified gene-protein associations for interleukin-6 receptor, chemokine CC-4, angiotensin-converting enzyme, and angiotensinogen. In 2014, Ramanan et al ([76](#_ENREF_76)) performed the first GWAS of amyloid PET using ADNI Florbetapir scans and reported that the *APOE* as well as *BCHE* genes were modulators of cerebral amyloid deposition together accounting for nearly 15% of the variance in amyloid deposition. Swaminathan et al (2014) reported that the association between plasma A and cortical amyloid deposition is modulated by *APOE* 4 status.

Two landmark case–control GWAS of AD, published as companion reports in *Nature Genetics* ([77](#_ENREF_77), [78](#_ENREF_78)), included the ADNI-1 data in their replication data sets. Hollingworth et al ([77](#_ENREF_77)) reported five novel risk variants: *ABCA7, MS4A6A/MS4A4E, EPHA1, CD33* and *CD2AP*, while Naj et al ([78](#_ENREF_78)) independently reported *CD2AP, EPHA1*, and *CD33* in addition to confirming the previously identified risk variants, *CR1, CLU, BIN1 and PICALM*. All variants identified in these reports have now been confirmed and make up a substantial proportion of the over 20 risk variants now identified for the disease ([79](#_ENREF_79)). The ADNI cohort was also included in studies of almost 30,000 individuals with MRI scans by the ENIGMA and CHARGE consortia ([80](#_ENREF_80), [81](#_ENREF_81)) Hibar et al 2014, Nature [under revision]). These studies found common variants influencing hippocampal volume, brain volume and numerous other subcortical volumes, measured from MRI; carriers and non-carriers of specific SNPs differed in hippocampal volume, on average, by an amount equivalent to about 3 years of normal aging.  Rhinn et al ([82](#_ENREF_82)) used an integrative genomic approach based on analysis of transcriptional networks in the human brain to identify candidate genes predicted to mediate transcriptional changes in carriers of the *APOE* 4 allele. Two genes of interest that affect amyloid deposition and age of onset in *APOE*4 carriers, *FYN* and *RNF2 19*, were subsequently confirmed using a meta-analytic GWAS using ADNI data. Lambert et al ([83](#_ENREF_83)) performed a meta-analysis of 74,046 individuals including the ADNI cohort, and identified 11 new susceptibility loci for Alzheimer's disease. ADNI also played a prominent role in the largest GWAS of human memory to date including the NIA Health and Retirement Study cohort plus ADNI, ROS/MAP and other samples (Ramanan et al *in press*). This GWAS implicated the *FASTKD2* gene for both episodic memory and hippocampal structure on MRI and nominated this gene as a potential neuroprotective target.

Numerous discovery, replication and methods publications using ADNI genetics data continue to appear from groups around the world at an accelerating pace. Overall, the papers outlined above along with dozens of other reports using multidimensional phenotypes from several ADNI data sets, have confirmed key findings in the genetics of AD and also identified a number of novel candidate genes warranting further investigation in independent cohorts.

ADNI review

The proliferation of papers published using ADNI data is undoubtedly a measure of the success of the initiative. However these studies represent a sometimes overwhelming volume of information to the average researcher. The review of ADNI papers by Weiner et al ([5](#_ENREF_5)) and its update ([42](#_ENREF_42)) summarized this research and enabled researchers to avoid unnecessary duplication of efforts and to determine where future directions might lie.

ADNI has provided a model for similar neuroimaging projects around the world

ADNI has provided a model for neuroimaging initiatives worldwide run under the direction of the umbrella organisation, Worldwide ADNI (WW-ADNI), sponsored by the Alzheimer's Association. Programs utilizing ADNI methodologies have been established in Japan, Australia, Argentina, Taiwan, China, Korea, Europe, and Italy ([84](#_ENREF_84)) with the common goals of harmonizing protocols and results internationally and sharing standardized data across the international research community. It is hoped that WW-ADNI approaches will establish internationally recognized standards for the identification and diagnosis of AD and document cognitive and physical changes that occur throughout disease progression in diverse ethnic groups.

WW-ADNI initiatives share the use of established ADNI protocols for structural MRI, PET, and the collection of cognitive, blood and genomic data but differ in cohort size and composition, and in the emphasis of some studies. Three international initiatives were established shortly after North American ADNI. European ADNI (E-ADNI) began as a pilot study and has now expanded to a network of 50 sites across Europe with a particular focus on standardization of protocols for measuring hippocampal volume ([85-87](#_ENREF_85)). In conjunction with E-ADNI, the European Union funded the informatics infrastructure, neuGRID and its successor, neuGRID for You (N4U) which have been designed to be interoperable with the LONI data repository. Neuroimaging data from Australian ADNI, also known as the Australian Imaging Biomarkers and Lifestyle Flagship Study of Aging (AIBL), established in 2006, has also been made available through LONI. AIBL is a long-term longitudinal investigation sharing many of the same goals as ADNI but with a particular emphasis on examining various health and lifestyle factors and their effect on cognitive decline ([88](#_ENREF_88)). AIBL data have resulted in over 80 publications including a recent work which described a panel of blood-based biomarkers able to accurately predict conversion of MCI patients to AD ([89](#_ENREF_89)). Japan ADNI was established in 2007 enrolling 600 participants and using a research protocol designed to maximize compatibility with North American ADNI ([90](#_ENREF_90)). Cognitive, structural MRI, FDG and amyloid PET data from J-ADNI correlates well with that from North American ADNI, perhaps reflecting the similar demographics of the two initiatives. However J-ADNI has reported a rate of MCI to AD progression nearly double that observed in the North American initiative ([84](#_ENREF_84)).

Since 2010 four additional initiatives have been established in Taiwan, Korea, China and Argentina. These projects are in various initial stages of establishing infrastructure and enrolling participants and are modelled largely on the North American initiative. One significant difference in Korean ADNI is the focus on vascular risk factors on Alzheimer's disease progression as Subcortical Vascular Dementia is more prevalent in Asian dementia patients ([84](#_ENREF_84)).

Results from AIBL, E-ADNI and J-ADNI prove that the ADNI model is highly effective and able to be transposed to many settings around the world. It is expected that the initiatives in Korea, Taiwan, China and Argentina will also make important contributions to painting a global picture of AD disease progression. WW-ADNI is the result of an unprecedented degree of international cooperation. The willingness of scientists worldwide to participate in open data sharing will play a key role in the identification and development of disease modifying and preventive treatments for AD.

ADNI has inspired other projects to investigate AD risk factors

The development of ADNI infrastructure, methodologies and data collection techniques has facilitated the establishment of additional projects investigating specific risk factors in different populations.

DOD-ADNI

Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are well-known risk factors for AD ([91-93](#_ENREF_91)). Military veterans in particular have elevated risks of both TBI and PTSD over the course of their service due to combat and other exposures. Funded by the Department of Defense, a new study termed DOD-ADNI is investigating whether TBI and/or PTSD and veterans increases the risk for AD and decreases cognitive reserve ([94](#_ENREF_94)). This longitudinal study uses ADNI methodology to obtain baseline and one year measurements of AD pathophysiological markers, medial temporal brain atrophy, and cognitive function in three groups of veterans: those with a history of TBI (with or without PTSD), those with ongoing PTSD (without TBI), and control subjects comparable in age, gender, and education ([94](#_ENREF_94)). DOD-ADNI is being conducted across a number of established ADNI sites. A future study will examine the same questions in veterans with MCI and TBI/PTSD.

ADNI Depression study

One of the most debilitating aspects of Late Life Depression (LLD) is the cognitive impairment suffered by up to 60% of individuals. Accelerated cognitive decline in LLD is likely the result of multiple factors including hypoperfusion, amyloid deposition, cortical atrophy, white matter signal hyperintensities, and genetic susceptibility.  In the past, determining the specific mechanisms contributing to cognitive impairment in LLD has been challenging due to the co-occurrence of neurodegenerative disease and methodological limitations related to small sample sizes. The ADNI Depression Study (ADNI-D) aims to clarify the degree to which these distinct mechanisms are associated with accelerated rate of cognitive decline in LLD. This longitudinal study will use standardized ADNI methods and data-sharing protocols, enrol participants who meet criteria for LLD or Major Depression at 2 established ADNI sites, and compare these participants to ADNI-2 control subjects.

ADNI has inspired other initiatives unrelated to AD

As an example of an extremely successful public-private partnership in the neurosciences that lies in the precompetitive space, ADNI has served as an impetus for a coordinated and focused process of biomarker development across multiple therapeutic areas. By proving the feasibility of a multi-site study aimed at developing biomarkers to track disease pathophysiology for subsequent use in clinical trials, ADNI has directly inspired other initiatives focusing on different neurodegenerative diseases.

Parkinson’s Progressive Markers Initiative

The Parkinson's Progressive Markers Initiative (PPMI) was launched in 2010 with the aim of identifying biomarkers for Parkinson disease (PD) progression to improve the understanding of disease pathophysiology and to facilitate more efficient PD modifying therapeutic trials ([40](#_ENREF_40)). This observational, international, multicenter study was based largely on ADNI, employing a largely similar structure, organization and funding as a public – private partnership initiated by the Michael J Fox Foundation for Parkinson's Research. PPMI and ADNI share the same LONI Data Informatics core headed by Arthur Toga, and Fluid Biomarker core headed by John Trojanowski and Leslie Shaw. In addition, ADNI has contributed many of its standardized methodologies to PPMI, especially in the analysis of certain CSF biomarkers. Like ADNI, PPMI’s data and samples are freely available to qualified researchers. PPMI data are already being downloaded extensively with 192,458, 57,024, and 561 downloads of image, clinical, and genetic data, respectively, by 645 distinct downloaders as of July 2014 (Arthur Toga, personal communication). PPMI has quickly generated significant results with an initial biomarker paper reporting the prognostic and diagnostic potential of CSF biomarkers in early-stage PD ([95](#_ENREF_95)).

Frontotemporal Lobar Degeneration Neuroimaging Initiative

ADNI infrastructure forms the basis of the recently established Frontotemporal Lobar Degeneration Neuroimaging Initiative (FLDNI) which aims to determine the optimum methods (MRI, FDG-PET, and biomarker measures) for following the progression of FTLD. This longitudinal study hopes to identify brain regions in which changes in metabolism and structure occur in this common cause of dementia.

North American Registry for Care and Research in Multiple Sclerosis

ADNI is also the prototype for the North American Registry for Care and Research in Multiple Sclerosis (NARCRMS), announced in May 2014 and slated to be launched in 2015. This public-private partnership aims to track disease progression in multiple sclerosis (MS), identify new biomarkers and compare therapeutic outcomes. Participating doctors will use standardized methodologies to collect and report information on their MS patients including biomarker levels, demographic and clinical data and imaging test results. Like the ADNI database, the NARCRMS database will have open access for patients, physicians and industry ([41](#_ENREF_41)).

Down Syndrome Biomarker Initiative

Another recent study structured largely on ADNI is the Down Syndrome Biomarker Initiative ([96](#_ENREF_96)), which aims to investigate the link between Down Syndrome and AD. This 3 year pilot study is currently being run at UC San Diego under the auspices of the Alzheimer’s Disease Cooperative Study (ADCS) with pharmaceutical funding. Twelve participants are undergoing specialized cognitive testing, retinal amyloid imaging, brain PET amyloid imaging, structural MRI, and screening for promising blood biomarkers. It is hoped that this initial investigation, launched in March 2013, will pave the way for a much more extensive study using many of the hallmarks of ADNI structure and standardized methods.

ADNI’s next step: tau PET imaging and ADNI-3

During the past two years, several PET ligands which have reasonable sensitivity and specificity to detect tau tangles in the living human brain have been developed ([97-104](#_ENREF_97)). Numerous clinicopathological studies have established that the amount and distribution of tau tangles correlate with cognitive impairment and severity of dementia ([105-109](#_ENREF_105)). Preliminary reports with tau PET appear to confirm the view that the extent and location of tau correlates with severity of cognitive impairment ([101](#_ENREF_101), [110](#_ENREF_110), [111](#_ENREF_111)). This suggests that tau PET has the potential to become a ‘surrogate outcome measure’ for AD clinical trials, which would greatly facilitate and accelerate all such trials. A large scale longitudinal observational study of tau PET would be the next step towards development of a surrogate outcome measure, which could ultimately be approved by the FDA and other regulatory agencies.

ADNI has been granted funding from the Department of Defense to conduct tau PET studies at baseline and after one year using DOD ADNI subjects in addition to a subset of cognitively normal, MCI and AD ADNI-2 subjects. It is expected that results from this study will provide pilot data for a competitive renewal of ADNI-2, termed ADNI-3. If funded, ADNI-3 would run for 5 years (2016-2021) and would enrol new subjects in addition to continuing to follow subjects currently enrolled in ADNI-2. Subjects would undergo longitudinal tau PET scans, as well as the current ADNI-2 amyloid PET, FDG PET, MRI (including structural, perfusion, resting state fMRI, and diffusion tensor imaging) scans. Planning for ADNI 3 will continue up to submission of the proposal in November 2015.

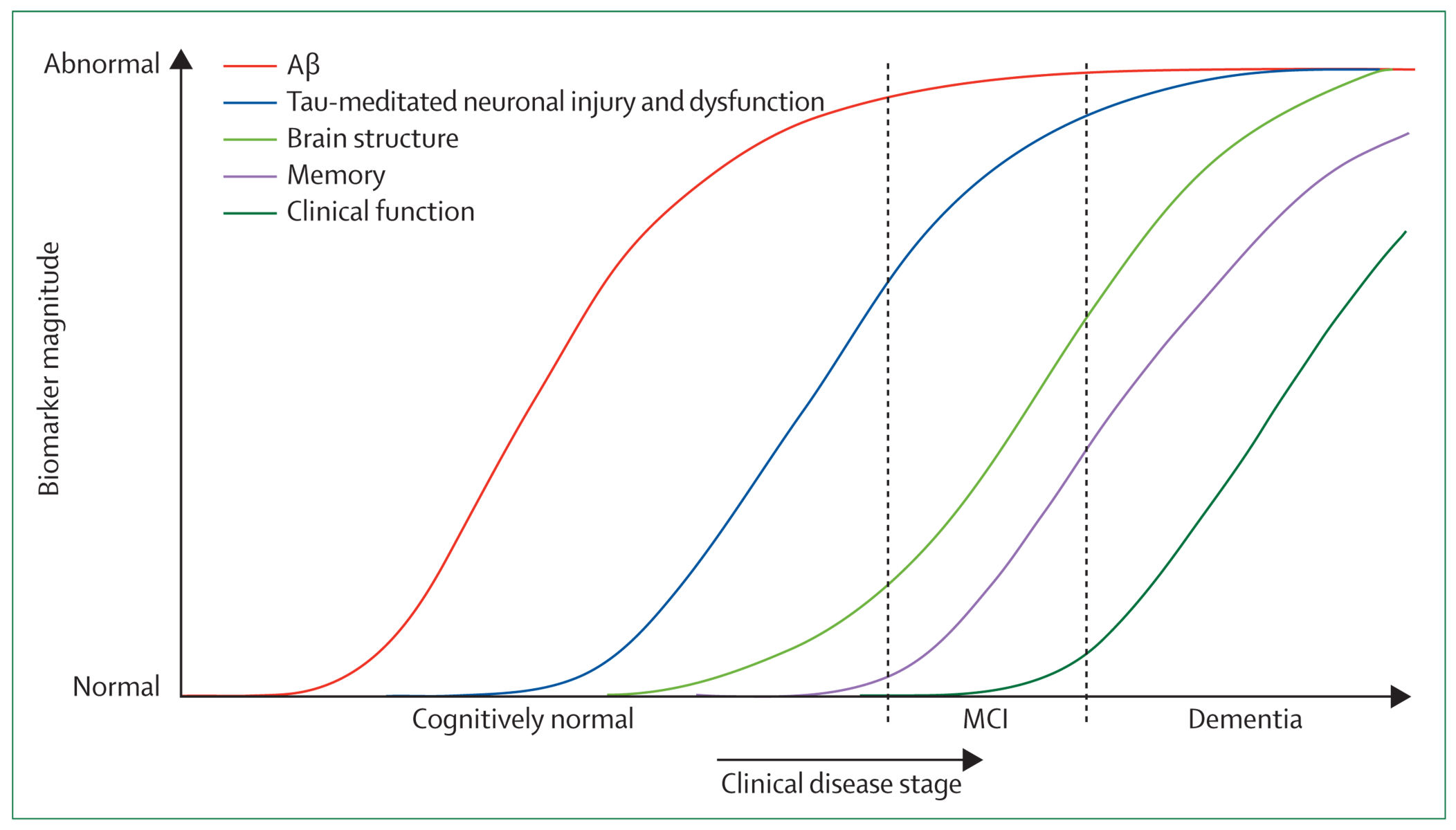
### Conclusions

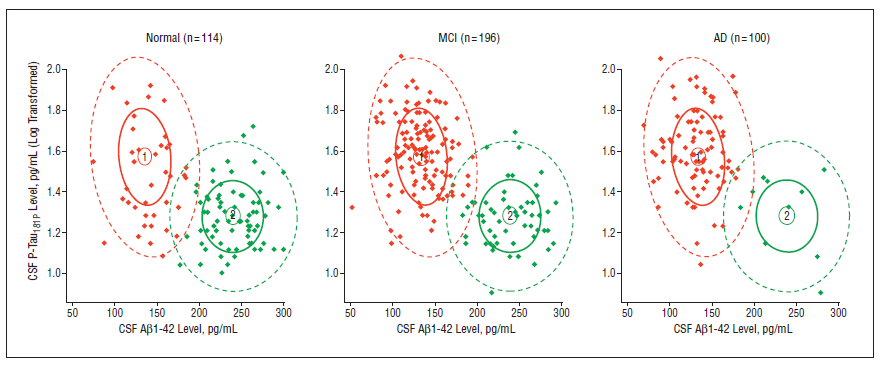
The original and continuing goal of ADNI has been to validate biomarkers for AD clinical trials. By all accounts ADNI has accomplished this goal, and helped established the critical diagnostic role of amyloid phenotyping. ADNI has demonstrated the feasibility and impact of large scale data sharing without embargo to the extent that it now serves as the model for other programs wishing to openly share data. ADNI is a model of a successful public-private partnership and this structure combined with ADNI’s development of standardized protocols for use in multicenter settings has inspired other initiatives aimed at evaluating additional AD risk factors, and at developing biomarkers for other diseases. ADNI has also helped to establish a world-wide network of AD clinical trial sites. Research using ADNI data has generated over 600 publications in a decade and has significantly advanced our knowledge of the progression of AD pathology and of genetic risk factors for the disease. The recent piloting of tau imaging technologies augurs well for a second outstanding decade of innovation and progress.

### Figures

### http://www.supertechx-ray.com/pics/MRI/MagphanADNI-1small.jpg

Figure 1. The ADNI phantom

Figure 2: A model for biomarker dynamics in AD pathogenesis

Figure 3: A CSF biomarker signature for AD. Signature 1 (red) is AD, signature 2 (green) is the healthy signature.

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