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The Worldwide Alzheimer's Disease Neuroimaging Initiative: An update

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Abstract The Alzheimer's Disease Neuroimaging Initiative (ADNI), launched in 2004, has worked to accelerate drug development by validating imaging and blood/cerebrospinal fluid biomarkers for Alzheimer's disease clinical treatment trials. ADNI is a naturalistic (nontreatment) multisite longitudinal study. A true public-private partnership, the initiative has set a new standard for data sharing without embargo and for the use of biomarkers in dementia research. The ADNI effort in North America is not the only such effort in the world. The Alzheimer's Association recognized these global efforts and formed Worldwide ADNI (WW-ADNI). By creating a platform for international collaboration and cooperation, WW-ADNI's goals are to harmonize projects and results across geographical regions and to facilitate data management and availability to investigators around the world. WW-ADNI projects include those based in North America, Europe, Japan, Australia, Korea, and Argentina.

Keywords: Alzheimer's disease; Neuroimaging; Biomarkers; Cerebrospinal fluid

1. Introduction

When the Alzheimer's Disease Neuroimaging Initiative (ADNI) commenced in October 2004, it aimed to take advantage of improvements in imaging technology, genetics research, internet-based communication, and other fields to accelerate the development of treatments for preventing Alzheimer's disease (AD) or moderating its progression. ADNI researchers were tasked to achieve this effort by uncovering key biomarkers in the brain, blood, and cerebrospinal fluid (CSF), and cognitive and other clinical changes, that would characterize Alzheimer's at different stages of the disease. ADNI is the largest longitudinal, naturalistic study measuring magnetic resonance imaging (MRI), positron emission tomography (PET), genetic, and CSF biomarkers for AD, and it has the distinction of making all its data available to qualified investigators without embargo.

It should be emphasized that North American ADNI (NA-ADNI), and all other ADNI projects, are not treatment trials. They are naturalistic observational studies designed to mimic or stimulate treatment trials. The data obtained from ADNI can then be used to design improved treatment trials by pharmaceutical companies, government-funded investigators, or other research entities.

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Table 1
Leading ADNI programs

Enrolled participants					
Program site	W/AD-D	W/MCI	Normal	w/Memory concerns	Achievements and future goals
North America (NA-ADNI: ADNI-1, ADNI-GO, ADNI-2) 2004 to present www.adni-info.org/ adni.loni.usc.edu/	c.370	c.550	c.380	c.100	Helped establish PET tracers ^{11}C-labeled Pittsburgh Compound (PiB) and ^{18}F-labeled florbetapir as useful tools for detecting early stage AD pathology. Used novel MRI techniques to identify AD-related white matter microhemorrhages and axonal damage. Used genome wide association studies (GWAS) to identify novel AD genes and gene loci that may promote AD risk. Helped establish hippocampal volume as an AD biomarker. Promoted policy of open data sharing. The next phase, ADNI-3, is scheduled to begin in 2016.
Europe (AddNeuroMed) 2005–2008 www.centroalzheimer.org/ sito/ip_eadni_e.php	176	315	225		Identified novel AD biomarkers, including cortex thickness, plasma proteins involved in complement and coagulation pathways, and plasma levels of transthyretin protein. Developed novel approaches for discriminating between AD and HCs and for predicting AD progression, including the use of cortical thickness, *APOE*-genotype, and demographic information.
Europe (E-ADNI) 2005 to present www.centroalzheimer.org/ sito/ip_eadni_e.php	0	147	0		Using MR procedures and cognitive evaluations, investigators differentiated amnestic MCI (aMCI) participants with and without amyloid burden based on CSF Abeta42. Amyloid-positive group performed worse on certain cognitive assessments and showed a higher prevalence of *APOE* ε4 than did amyloid-negative participants.
Japan (J-ADNI) 2007 to present www.j-adni.org/etop.html	152	239	154		Found with MRI and PET that participants' conversion rate from aMCI to AD was ∼80% higher than that observed in NA-ADNI. Hippocampal atrophy rates and CSF amyloid levels were comparable between the two groups. The next phase, J-ADNI-2, is scheduled for launch in 2015.
Australia (AIBL) 2006–present aibl.csiro.au	291	234	397	616	Found that AD conversion risk in a healthy older cohort was most associated with a positive Aβ PET scan and a clear amnestic deficit. The positive scan may occur 15–20 years before a diagnosis of mild dementia. Also showed that *APOE* ε4, brain-derived neurotrophic $_{val/met}$ (BDNF$_{val/met}$) allele, and small hippocampal volumes were linked to faster cognitive loss in Aβ-positive normal adults. Future efforts will use PET imaging to identify links between tau aggregates and AD risk.
Argentina (ARG-ADNI) 2013 to present adni.loni.usc.edu/ study-design/ collaborative-studies/ argentina-adni/	13	28	15		Is revealing links between AD-related changes in cognition, structural brain changes, and protein biomarkers. Results indicate that baseline amyloid deposition by PIB-PET scan, left hippocampal volume changes, and memory performance separate the study's AD, MCI, and healthy participant groups. Now working to increase its study cohort by 100 members.
Korea (K-ADNI) 2013–present http://K-ADNI.org	150* planned	300† planned	50 planned		Plans to evaluate the effects of vascular risk factors on the development and progression of AD and subcortical vascular dementia.

Abbreviations: W/, with; AD-D, Alzheimer's disease-dementia; MCI, mild cognitive impairment; GO, Grand Opportunities; HC, healthy controls; CSF, cerebrospinal fluid; PET, positron emission tomography; Aβ, amyloid beta.

*Number includes 50 participants with AD and 100 with subcortical vascular dementia.

†Number includes 200 participants with MCI and 100 with vascular MCI.

2. Worldwide ADNI

Established in 2006 and managed by the Alzheimer's Association, WW-ADNI is an umbrella organization bringing together ADNI's from across the globe (Table 1). WW-ADNI provides a platform for the sharing of data and information among the various ADNI researchers with the primary goal of harmonizing protocols and results, such that a person who is tested in Europe, for example, would get the same results if tested with ADNI protocols in North America. WW-ADNI also works to harmonize data management and encourage open access to comparable worldwide data. This update provides reports from the WW-ADNI members who continue to strive to achieve the WW-ADNI goals.

2.1. North American ADNI

The first phase of NA-ADNI, now known as ADNI-1, was funded by a public-private partnership [1,2] of the National Institute on Aging, the National Institute of Biomedical

Imaging and Bioengineering, the National Institute of Mental Health, the National Institute for Alcohol Abuse and Alcoholism, the U.S. Food and Drug Administration, private pharmaceutical companies, and nonprofit philanthropic organizations that include the Foundation of the National Institutes of Health, the Alzheimer's Drug Discovery Foundation, and the Alzheimer's Association. ADNI-1 ran for 6 years, and it was followed by two subsequent phases: ADNI "Grand Opportunities" (ADNI-GO), which began in 2010; and ADNI-2, which was based on a competitive renewal of the original grant and began in 2011.

ADNI-1 established an organizational structure that continues today under ADNI-2. It contains eight separate "cores," each of which focuses on a particular aspect of the initiative: biomarkers, biostatics, clinical factors, genetics, informatics, neuropathology, MRI research, and PET studies. The cores operate under the auspices of an executive committee, with additional input from industry partners [1], and are hosted by >56 facilities around the United States and Canada. Their accomplishments have been considerable and diverse, and they have gone beyond the original goals of the initiative: impacting the industry-wide practice of open data-sharing, discovering genes that promote AD risk, and helping to establish other initiatives aimed at developing therapies for dementia [3].

The Clinical core recruited and assessed about 820 participants in ADNI-1, and they have enrolled nearly 600 more in the ANDI-GO and ADNI-2 phases [4]. All centers across the United States and Canada used identical criteria (available at http://www.adni-info.org/Scientists/ADNIStudyProcedures.aspx) to enrol subjects who are cognitively normal controls, who are cognitively normal with subjective memory complaints, and who have been diagnosed with early and late mild cognitive impairment and dementia [5]. It should be noted that different analyses of data generated by ADNI have used various fractions of this cohort. Clinical core members acquire baseline and longitudinal data from clinical examinations, cognitive tests, and other assessments.

The Neuropathology core conducts examinations at autopsy to validate or explain the clinical diagnoses, biomarker findings, and neuroimaging results of other ADNI cores. These autopsies have not only confirmed diagnoses of AD, they have also indicated a high rate of mixed pathologies among study participants, in accordance with previous studies [6–8]. AD was often detected alongside dementia with Lewy bodies (DLB), agyrophilic grain disease (AGD), hippocampal sclerosis, TDP-43, or mild small vessel disease [9,10]. In particular, the high prevalence of coincident DLB has identified alpha-synuclein, DLB's chief molecular suspect, as a potential biomarker in AD [11,12].

Three other cores, the MRI, PET, and Biomarker cores, have standardized the assessment procedures for use in all ADNI facilities. Such work has enabled them to better compare data obtained in multiple settings and with different varieties of scanners or hardware. The MRI core has obtained important information through the use of emerging MRI-related technologies. For example, it has used gradient echo sequences to detect microhemorrhages (MH) in cortical gray matter [13]. MH prevalence appears to increase with age and amyloid beta (Aβ) load. The core has also used diffusion tensor imaging (DTI) to identify axonal damage [14], and arterial spin labeling (ASL) to detect perfusion. The PET core has developed protocols for PET imaging of Aβ with different tracers: the ^{11}C-labeled Pittsburgh Compound B (PiB) and, more recently, the ^{18}F-labeled florbetapir. The core established that these tracers accurately reflect amyloid burden and are a useful tool for detecting early stages in the disease [15]. In contrast, it found that abnormal glucose metabolism measured by fluorodeoxyglucose PET (FDG-PET) occurs later in disease progression and may not be specific to AD [16]. The Biomarker core has reviewed the clinical performance and analytical use of CSF biomarkers [17], and it has initiated studies to develop effective plasma-based biomarkers [18]. The core has also curated a collection of CSF, serum, and plasma samples from over 700 ADNI participants; and it has assessed ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS-MS) as a novel technique for detecting AD through CSF- and blood-related abnormalities. The AlzBio3 immunoassay in current use is precision based, not accuracy based, and it is limited by differences in epitope recognition by differing antibodies and matrix effects. The UPLC-MS-MS assay has exceeded requirements for sensitivity in detecting AD and for specificity in discriminating other forms of dementia. It is also reproducible and accurate, and it may provide an antibody-independent alternative for the detection of Aβ42 [19,20].

The Biostatistics core, the statistical arm of NA-ADNI, has compiled a wide range of longitudinal data from ADNI participants—from baseline to as many as 7 years of follow-up. It has also plotted change over time for various biomarkers and neurocognitive tests [21]. These data have provided for numerous studies supporting Jack et al.'s model of biomarker dynamics during disease progression [21–25], and also for a few studies that contradict aspects of the model [26–28].

The Genetics core has been at the forefront of conducting genome wide association studies (GWAS) that leverage quantitative imaging and biomarker phenotypes. These efforts have led to the confirmation of several AD risk genes and the identification of novel risk loci, either alone [29] or as part of larger data sets provided by such consortia as Enhancing Neuro Imaging Genetics Through Meta Analysis or Cohorts for Heart and Aging Research in Genomic Epidemiology [30,31]. Further refinements to GWAS have included pathway and network analyses [32–34], the use of proteomics [35], and whole exome data [36], and copy number variant analysis. The latter refinement, in particular, has identified novel candidate AD susceptibility loci [37–39]. Overall, these novel bioinformatic strategies reflect an increasing understanding of the biochemistry of AD and have helped narrow the search for AD risk alleles.

The Informatics core of ADNI, formerly known as the Data and Publications core, has developed a sophisticated infrastructure to house its data repository, currently based at the Laboratory of Neuroimaging (LONI) at the University of Southern California. A ground-breaking feature of ADNI has been its policy of open data sharing, in which deidentified ADNI imaging, clinical, and genetic data are available to qualified researchers without embargo [40]. These data have now been downloaded by >3000 distinct researchers worldwide [41]. More than 600 publications have used and acknowledged the use of ADNI data, and they are therefore defined as "ADNI studies." These have been summarized in a series of reviews, currently covering papers to the end of 2013 [41–43]. Access to ADNI data and the publication of manuscripts are overseen by the Data and Publications Committee.

Collectively, the efforts made by NA-ADNI have made a significant impact on how clinical trials and other AD studies are conducted. Amyloid phenotyping for the identification of AD pathology using amyloid PET scans and CSF measurements is now an established approach in observational studies and treatment trials. Hippocampal volume has been approved as a biomarker by the European Medicines Agency, based in part on NA-ADNI data [44]. NA-ADNI's work with multiple imaging modalities has been used to devise required sample sizes for different participant groups in AD trials. Moreover, such work has also helped advance the accuracy of diagnostic classification [41]. Overall, the initiative's longitudinal design is proving a powerful tool for improving predictive and diagnostic accuracy [41].

The achievements of NA-ADNI have inspired similar initiatives that are modeled on ADNI structure, have similar data sharing policies, and use ADNI standardized methods. For example, there are currently three U.S. Department of Defense grants investigating the effects of traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) in Vietnam Veterans on the development of AD [45,46]. Other initiatives are investigating depression as a risk factor for AD, whereas still others seek to find biomarkers for AD-related diseases such as Parkinson's disease [47] and multiple sclerosis [48].

Based on the continued success of NA-ADNI, the initiative's team is preparing to submit a competitive renewal of ADNI-2, termed ADNI-3, in the fall of 2015. The continuation of this project will allow pathophysiological changes leading to AD, believed to be part of a 15-year process, to be tracked and characterized in a large, well-characterized cohort. ADNI-3 will also continue the investigation of comorbidities in AD, including DLB. If funded, the project would begin in August 2016 and commence a 5-year study with an elderly participant group containing 40% with MCI, 20% with dementia due to AD, and 40% with no cognitive decline. All subjects would undergo clinical cognitive assessments, lumbar puncture for CSF measurements of amyloid, tau, α-synuclein, proteomics, and other proteins of interest, and imaging by MRI, amyloid PET, tau PET, and FDG-PET. All participants would be followed to autopsy. The MRI protocol would have two tiers: sites with state-of-the-art MRI scanners would run an advanced protocol, and sites without such capabilities would use less advanced "standard product protocols." CSF measurements would include a state-of-the-art platform for immune assays, and mass spectroscopy analysis of Aβ and possibly other proteins. Internet-based methods for recruitment and neuropsychological assessment might also be incorporated.

2.2. European ADNI and AddNeuroMed

European ADNI (E-ADNI), founded in 2005, was the first extension of ADNI beyond the North American study. It is part of a larger study entitled "Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development," or PharmaCog. The European Commission established PharmaCog to facilitate the drug development for AD. Toward that goal, E-ADNI is PharmaCog's work package 5 (WP5), one of the project's four main modules, aimed to validate and qualify biomarkers that are sensitive to disease progression.

E-ADNI researchers have assessed and refined their initiative's imaging procedures. Sixty-five elderly volunteers have been studied to calibrate 13 3-Tesla (3T) MRI scanners to collect high-resolution T1-weighted images and other data. They also conducted several reliability assessments. Structural MR procedures were tested for their ability to detect such morphometry data as cortical thickness and subcortical volumes, and the results showed acceptable reproducibility [49]. An analysis of multisite diffusion MR procedures showed good reliability when assessing white matter data [50]. Good reproducibility was also found in test-retest studies of the default mode network (DMN) using functional MRI (fMRI) [51,52]. Moreover, the results of these fMRI studies suggest that DMN extraction is largely insensitive to physiological noise [52].

The Clinical core of E-ADNI has enrolled 147 participants with amnestic MCI (aMCI), about half of whom are amyloid positive. All individuals have undergone CSF collection at baseline and a serial assessment of clinical, neuropsychological MR, blood, electroencephalogram, and CSF biomarkers every 6 months. The last follow-up assessment is scheduled by the end of June 2015. By following the NA-ADNI recruitment protocol, E-ADNI has built a remarkably similar cohort [53]. Assessments of participant data indicate that amyloid-positive individuals had poorer global cognition, immediate verbal memory, visual memory, and working memory compared with amyloid-negative aMCI participants. The amyloid-positive group also had a significantly higher prevalence of the *APOE* ε4 allele. By contrast, functional, mood, and behavioral features were similar between the two groups. Incident AD dementia has remained about 10% per year and drop outs also about 10% per year.

AddNeuroMed was another cross-European public-private partnership developed for AD biomarker discovery

that used ADNI protocols and phantoms. Officially ended in 2008, AddNeuroMed produced a number of studies by merging data with NA-ADNI; and it encompassed six sites in Europe with a total of 716 participants. The project's goal was to get as much information as possible from blood samples through the use of proteomics, metabolomics, genomics, and transcriptomics; and to combine these data with imaging data. According to several AddNeuroMed studies, the combination of multiple MRI estimates [54] with CSF [55] and plasma measures [56,57] showed improved AD classification and prediction accuracy compared with single MRI measures.

AddNeuroMed researchers also developed novel approaches for discriminating between AD and healthy controls (HCs) and predicting AD progression. A random forest model that combined cortical thickness and volumetric measures reached an AD/HC sensitivity/specificity of 89%/92%. When *APOE*-genotype and demographics information (age, sex, and education) were added, the model attained an MCI-to-AD-conversion sensitivity/specificity of 83%/81% [58]. In another study, multivariate ordinal regression applied to baseline structural MRI scans showed an accuracy of 82% in distinguishing HC-like (people with HC and stable MCI) from AD-like (MCI converters and those with AD), and an accuracy of 70% in predicting conversion at 12 months [59]. Two other efforts used orthogonal partial least squares to latent structures, a multivariate analysis technique, to classify subjects with AD and HC. The classifier models involved cortical thickness measures and subcortical volumes in the first study [60] and hippocampal subfield volumes in the second study [61]. In the first case, the classifier performed with 84% sensitivity and 91% specificity, and its prediction of conversion from MCI to AD at 12 months was 91% [60]. The combination of the hippocampal subfields volumes achieved an AD/HC classification accuracy of 82% and a prediction accuracy of 81% [61].

Still other AddNeuroMed efforts published data investigating several biomarkers for AD. These included entorhinal cortex thickness [62], plasma proteins involved in the complement and coagulation pathways [63], and plasma levels of the protein transthyretin [64]. In addition, project studies identified new panels of plasma proteins that were able to predict the conversion to dementia from the prodromal stage [65,66].

2.3. Japanese ADNI

With government funds from the Japanese Ministries of Health, Labor and Welfare and the New Energy and Industrial Technology Development Organization (a foundation of the Ministry of Economy, Technology, and Industry), Japanese ADNI (J-ADNI) was launched in 2007. As with NA-ADNI and E-ADNI, this initiative aimed to promote global clinical trials of disease-modifying therapies for AD. The operation of J-ADNI was greatly assisted by an industry scientific advisory board (J-ISAB), organized by 11 pharmaceutical companies and a group of seven imaging companies that formed "imaging ISAB."

The J-ADNI clinical study protocol was designed to maximize compatibility with that of the NA-ADNI, and it included structural MRI, fluorodeoxyglucose and amyloid PET, CSF sampling and *APOE* genotyping, and clinical and psychometric tests. The initiative's 38 sites enrolled 239 participants with aMCI, 152 with mild AD, and 154 cognitively normal individuals.

J-ADNI's MRI core has established an algorithm to standardize MRI scanning across different MRI equipment. This algorithm was based on the three-dimensional magnetization-prepared rapid gradient-echo protocol. Programs to improve image clarity and other factors were administered to enable accurate and reproducible volumetric analysis of structural MRI data [67]. The PET core has set up a standardized protocol for PET imaging in J-ADNI, and a versatile and rigorous quality control system of PET images. This system is being used as a standard procedure for all PET imaging in Japan. More than 60% of participants in 28 clinical sites were scanned by FDG-PET, and an in-depth analysis of the multicenter data has started [68–70]. Amyloid PET imaging using Pittsburgh Compound B (^{11}C-PiB) was conducted in ~15 sites; whereas two sites performed PET studies using ^{11}C-BF-227. The Biomarker core established the J-ADNI biosample repository at Niigata University, collecting biofluid samples through a nationwide network. Blood samples were collected from all participants at every visit, and ~35% of the participants (190 cases) underwent lumbar puncture for CSF samples. This latter procedure proved safe without any severe adverse events. The Biomarker core has also optimized procedures for the quantitation of samples.

Although the analysis of data from these studies has not been completed, a couple of interesting preliminary results are being obtained. For example, the conversion rate of aMCI individuals to AD appears to be ~80% higher than those in the NA-ADNI, and at a similar level to that of participants with late aMCI from the U.S. National Alzheimer's Coordinating Center and the Australian ADNI. Yet the rates of hippocampal atrophy appear to be comparable between participants in J-ANDI and those in NA-ADNI. In addition, lower CSF $A\beta_{1-42}$ levels were in good accordance with positive amyloid PET scans, a finding also determined in NA-ADNI.

The second phase of J-ADNI (J-ADNI-2) is scheduled for launch in 2015. It aims to focus on populations with very early stages of AD, including preclinical AD and early/late amnestic MCI. To recruit preclinical AD participants, ~700 cognitively normal older individuals will undergo amyloid PET imaging at 31 PET sites with one of the three tracers (^{11}C-PiB, ^{18}F-florbetapir, or ^{18}F-flutemetamol), allowing the selection and enrollment of 150 cognitively normal, Aβ-positive individuals that meet the criteria of preclinical AD. This cohort will then be followed-up once a year for 3 years. The clinical protocol includes paragraph

recall, the Mini-Mental State Examination, the free and cued selective reminding test, and digit symbol (ADCS-preclinical Alzheimer Cognitive Composite) tests.

The MCI study of J-ADNI-2 is devoted to the longitudinal investigation of early and late amnestic MCI, according to the criteria used by NA-ADNI-2. CSF sampling and amyloid PET imaging, structural MRI using 3T scanners, and any of the three optional assessments (resting state fMRI, ASL, or DTI) will be performed in all participants with normal cognition, preclinical AD, and early/late MCI. The data from both J-ADNI and J-ADNI-2 will establish the basis for upcoming clinical/prevention trials of disease-modifying drugs for MCI due to AD and preclinical AD.

2.4. Australian ADNI

Australian ADNI, better known as the Australian Imaging, Biomarkers and Lifestyle Study of Aging (AIBL), was launched in 2006. It has completed 6 years of follow-up (at 18 month intervals) on the original cohort of 1112 participants. About 70% of this cohort comprised of normal controls, with an average age of entry at 70 years; although the remainder comprised of participants with MCI or AD [71]. Data have been collected on demographic and lifestyle factors, cognitive function, imaging and blood biomarkers, and genomics [71]. Serial Aβ PET and MRI were initially limited to 288 participants [72], but the cohort was enlarged in 2012 to 2013 and imaging was offered to all participants. Total enrolment is now >1500, and the follow-up assessments for additional enrollees are ongoing.

Two major strengths of AIBL are the extensive use of Aβ PET imaging from commencement and the inclusion of a large number of healthy older participants. These factors have provided insights into the cognitive, genetic, and amyloid-related changes that may lead to AD. For example, AIBL was able to demonstrate the strong relationships between age, carriage of *APOE* ε4, and the prevalence of a positive amyloid scan (Aβ+) [72]. AIBL also found that cognitive performance did not differ significantly between normal older individuals who were or were not Aβ+, though such performance tended to be lower in Aβ+ females. However, a clear decline in episodic memory function could be detected over 3 years in the Aβ+, whereas those with negative Aβ scans showed no such decline. AIBL also demonstrated that *APOE* ε4 [73], brain-derived neurotrophic$_{val/met}$ allele [74], and small hippocampal volumes [75] are all associated with faster cognitive decline in Aβ+ normal individuals; although tertiary educational achievement raises, and small vessel cerebrovascular disease lowers, baseline cognitive performance without influencing the rate of decline in Aβ+ individuals. Many of these findings have been used in the design of early intervention trials such as the Anti-Amyloid therapy trial in Asymptomatic Alzheimer's disease (The A4 Study). AIBL investigators in Melbourne will contribute to this trial, the only A4 Study site outside of North America.

Another key aim of AIBL has been assessing the progression from MCI to AD in its participant cohort. Much of this work has focused on the role of amyloid in AD conversion. Over 3 years, conversion risk in the cohort was associated most strongly with a positive amyloid scan (with an odds ratio of 15) and a clear amnestic deficit (odds ratio 11); and when both findings were present, the positive predictive value was 86% [75]. Using the vast amount of serial PiB scanning data, AIBL researchers were able to demonstrate that Aβ accumulation occurs at a rate of only 2% per year in Aβ+ individuals, and that it takes 20 to 30 years to build up Aβ levels to those found in mild AD subjects [76]. Furthermore, the PiB scan becomes positive 15 to 20 years before mild dementia, a decade before other imaging and cognitive tests become abnormal [76]. Accumulation of amyloid reaches a plateau at high amyloid burden; and as dementia advances, PiB binding then declines in some individuals [76]. All these findings have implications for drug trial design and the interpretation of how drugs affect amyloid burden.

Progress has also been made by AIBL in other areas of research: including the development of an AD blood-based biomarker and the study of lifestyle factors influencing AD risk. Several promising blood biomarker candidates have been identified [77–80], but they all require further validation before their clinical value is fully known. This effort, however, did lead to an incidental observation that anemia may be associated with AD [81]. Meanwhile, the lifestyle arm of AIBL has found that the risk reduction benefit of physical exercise for being Aβ+ is greater with high intensity exercise, particularly in *APOE* ε4 carriers [81]. Greater adherence to a healthy, Mediterranean-style diet is also more clearly associated with better cognitive performance in ε4 carriers [82].

AIBL imaging data and demographic data compatible with NA-ADNI is available on the LONI website. The initiative's infrastructure is now supporting recruitment for academic and industry-funded therapy trials, including the study of AD risk in Vietnam Veterans. AIBL will also begin using PET to image tau aggregates, in an effort to reveal novel links between tau burden and AD.

2.5. Korean ADNI

The Korean ADNI, commenced in 2013, is a 6-year national project that aims to study five representative groups in dementia: people with healthy brains, with MCI, with AD, with vascular MCI, and with subcortical vascular dementia (SVD). Funding for the initiative has come from both the government (the Korean Ministry of Health and Welfare) and private industry.

Five hundred participants will be recruited for the initial 2 years, and then followed up annually. Sixth month evaluation from baseline will also be performed to detect the earliest changes of progression markers. Twenty-five nationwide clinical sites are participating and the target numbers of

each group are 50 HCs, 200 individuals with MCI, 100 with vascular MCI, 50 with AD, and 100 with SVD. As with other ADNI initiatives, participants will be characterized and followed-up with clinical, neuropsychological, and MR imaging at every visit; and blood, CSF, and PET (FDG and amyloid imaging with 18F-flutemetamol) will be collected twice during the study period (at baseline and at 24 months).

A feature of K-ADNI that distinguishes it from other ADNI programs is its inclusion of individuals with either vascular MCI or subcortical vascular dementia. Multi-infarct dementia and vascular dementia with evident clinical strokes are excluded to maintain the homogeneity of vascular dementia subjects. Data collected (clinical, neuropsychological, MR, PET, and biomarkers) will be anonymized and shared with the WW-ADNI community by mirroring the current longitudinal online research and imaging system platform to the LONI website in the United States.

Given the relatively large proportion of Asian individuals affected by vascular dementia, the K-ADNI plans to evaluate the effects of vascular risk factors on the development and progression of AD and subcortical vascular dementia. The initiative was in the final stages of setting up its study infrastructure in 2014, and it is now starting to recruit subjects from clinical sites.

2.6. Argentina ADNI

The Argentina ADNI (Arg-ADNI) is the first ADNI center in Latin America and the first worldwide with primarily Hispanic community-dwelling participants. Since its creation in 2013, Arg-ADNI has established a network of interdisciplinary work among neurologists, psychiatrists, neuropsychologists, molecular biologists, neuroradiologists, and pathologists to adapt and optimize available clinical tools and technologies. It aims to improve understanding of the development and natural evolution of aging and AD in our setting. Arg-ADNI adopted the MRI, CSF and ^{11}C-PiB PET parameters of ADNI-2, and it designed neuropsychological tests to permit comparison with NA-ADNI data.

As of 2015, Arg-ADNI contains a cohort of 56 participants at a single institution in Buenos Aires. The investigators have completed baseline testing of their cohort and the first 12-month follow-up. All subjects underwent clinical assessment, 3T MRI scans, blood collection of immortalized lymphoblasts and *APOE* testing, FDG-PET scans, and ^{11}C-PiB PET scans. At least 80% of participants donated a sample of CSF via a lumbar puncture. Cross-sectional analysis of baseline data is revealing links between cognition, structural brain changes, and biomarkers. Among the 28 patients with MCI at baseline, three progressed to mild AD at 12 months for a progression rate of 10.7%. Baseline amyloid deposition by PIB-PET scan and left hippocampal volume separated the normal controls, MCI, and AD groups; and it correlated with memory performance, one of the core impairments across the disease's trajectory.

Arg-ADNI is now attempting to recruit and characterize another 100 individuals as part of its cohort. Its long-term goal is to establish and maintain a high-quality research infrastructure that can support a wide spectrum of interdisciplinary projects in Argentina.

2.7. Other worldwide sites

China ADNI (C-ADNI) is supported by the Chinese government and various industry collaborators, with initial start-up funds issued by the government and distributed to each participating site. The project began in 2012 at seven medical centers in Beijing. Several more centers have been added since then, and participant enrollment has begun [83,84]. C-ADNI intends to recruit and assess 800 to 1000 participants, including 200 to 250 cognitively normal controls, 400 to 500 individuals with MCI (early and late), and 200 to 250 with dementia [83,84]. Ultimately, they hope to add >90 study sites nationwide. As of 2015, C-ADNI has established a Clinical core, MRI core, PET core, Biomarker core, and Biostatistics core [85].

Taiwan ADNI was first organized by the Taiwan Dementia Society with five centers in northern Taiwan and began its initial 3-year longitudinal study in 2012. It planned to enroll 200 participants who were evenly split between cognitively normal control subjects and individuals with eMCI, late MCI, and AD. The project will eventually expand to additional sites in central and southern Taiwan.

Early stage ADNI efforts are expanding to other parts of the world including India and Brazil.

3. Industry involvement

NA-ADNI's Private Partner Scientific Board (PPSB) comprises private multinational companies, non-for-profit organizations, and one U.S. governmental organization (The Foundation of the National Institute of Health) to provide complementary funding for ADNI. This board also works to collaborate with the NA-ADNI steering and executive committees in efforts to better understand the disease and accelerate drug development. The PPSB established several scientific workgroups to address needs and gaps in the field. More detail on the PPSB and its role in ADNI-2 can be found in this issue of *Alzheimer's & Dementia* [86].

4. Summary

The bringing together of ADNI research efforts from across the globe under the WW-ADNI platform has yielded many benefits and continues to drive toward the overarching goals of harmonization and data sharing. ADNI methods are increasingly being recognized as the gold standard for the use of biomarkers in approved phase II and III AD clinical trials by the U.S. Food and Drug Administration and the European Medical Agency. WW-ADNI has broken down the traditional communication barriers by creating a platform

for collaboration and cooperation across geographical regions with academic, government and industry scientists. Future ADNI efforts such as NA-ADNI-3, should lead to a better understanding of the early stages of AD and the discovery of better tools for earlier diagnosis and will benefit the global Alzheimer's community.

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